# Toxicology Research Laboratory

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DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7M
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Title Page

Draft Report for Task Order No. UIC-7M

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

Sponsor: U.S. Army Medical Materiel Development Activity

Test Article: WR242511 Tartrate

Contract No.: DAMD17-92-C-2001

Study Director

Barry S. Levine, D.Sc., D.A.B.T.

In-Life Phase Completed On

July 26, 1994

Performing Laboratory

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This dose range-finding study evaluated the developmental toxicity of WR242511 tartrate in time- mated New Zealand female rabbits. Doses were 0, 1, 2.5, 6 and 14 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of mating). Maternal toxic manifestations included the fatalities of all animals at 14 mg base/kg/day by GD8 and all animals at 6 mg base/kg/day by GD12. In the 6 mg base/kg/day dose, activity was decreased in one animal the day prior to death. A marginal lack in weight gain and decrease in food consumption were observed at least in one of the surviving pregnant females in the 2.5 mg base/kg/day dose. The 2.5 mg base/kg/day dose was considered at or near the maternal no observable adverse effect level (NOAEL).

Fetal toxicity was seen in 2.5 mg base/kg/day as significant decreases in fetal body weights and one non-viable fetus. A biologically significant decrease in the female fetal body weights was observed at the 1 mg base/kg/day dose. The 1 mg base/kg/day dose was considered at or near the low observable adverse effect level for developmental toxicity. The results of this study and a previous dose range-finding developmental toxicity study in rats (UIC/TRL No. 143) suggested direct developmental toxicity of WR242511 tartrate, and a higher sensitivity in rabbits than rats. In addition, it was evident in rats and rabbits that there is an increased sensitivity of female fetuses to the test article in comparison to the males. The high dose for the definitive developmental toxicity study in rabbits should not exceed 3.5 mg base/kg/day to produce enough surviving females at the high dose to assess toxicity. Accordingly, 0.5, 1.3 and 3.5 mg base/kg/day are suggested as doses for the definitive developmental toxicity (segment II) study in rabbits.

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Signature Page

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RABBITS

TRL Chemical No.: 1720614

Sponsor: U.S. Army Medical Materiel
Development Activity
Fort Detrick
Frederick, MD 21702-5009

Test Article: WR242511 Tartrate

Sponsor
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Testing Facility: TOXICOLOGY RESEARCH LABORATORY (TRL)
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## 1. SUMMARY

This dose range-finding study evaluated the developmental toxicity of WR242511 tartrate in time-mated New Zealand White (Pasteurella Free) female rabbits. Doses were 0, 0.5, 1, 2.5, 6 and 14 mg base/kg/day administered by gavage during gestation days (GD) 6 - 18 (GD0 = day of observed mating). The doses were based on a preliminary dose range-finding study of WR242511 in non-pregnant rabbits and a dose range-finding developmental toxicity study in rats. The results of maternal and fetal toxic responses are summarized in Table 1. All animals in the 6 and 14 mg base/kg/day doses were dead by GD12. Changes in their reproductive indices (e.g. % total loss, % preimplantation loss) were a reflection of early maternal mortality. In the 2.5 mg base/kg/day dose, marginal maternal toxicity was indicated by biologically, but not statistically, significant decreases in food consumption at GD15 and GD18 (i.e. only towards the end of dosing), accompanied by a marginal loss of weight in one of these pregnant rabbits. The 2.5 mg base/kg/day dose was therefore considered at or near the low observable adverse effect level (LOAEL) for maternal toxicity.

Fetal toxicity was apparent in the 2.5 mg base/kg/day dose, and included one non-viable fetus. Biologically significant decreases in fetal body weights were also observed in this dose and in 1 mg base/kg/day female fetuses. This decrease was also statistically significant in the female fetuses at 2.5 mg base/kg/day. No other test article-related differences were observed in any other fetal parameters across groups. The 1 mg base/kg/day dose was considered at or near the low observable adverse effect level (LOAEL) in the fetuses. Accordingly, the following doses are recommended for the definitive developmental toxicity (Segment II) study in rabbits: 0, 0.5, 1.3 and 3.5 mg base/kg/day.

## 2. INTRODUCTION

This study was conducted to provide information for use in the selection of dose levels for a developmental toxicity (Segment II) study in rabbits. The test article was administered by daily gavage to time-mated females during gestation days 6 - 18. The fetuses were delivered by Cesarean section on gestation day 29 and were examined grossly for abnormalities. In addition, maternal toxicity was assessed during the study and reproductive indices were calculated. All methods and procedures in this study were conducted within the spirit of the Toxicology Research Laboratory, University of Illinois at Chicago Quality Assurance Program designed to conform with FDA Good Laboratory Practices Regulations. No unforeseen circumstances affected the integrity of the study. This study was stagger-started over two days and was initiated on June 26, 1994 (observation of mating). Dosing was initiated (stagger-started) on July 2, 1994 (GD6) and the in-life portion was terminated on July 26, 1994 (GD29).

## 3. MATERIALS AND METHODS

### 3.1 Test Article

WR242511 tartrate (Bottle Lot No. BM 05816), a fine, yellow powder, was received on June 16, 1993 from Hemer & Co. for this study, and was previously assigned an in-house chemical number (1720614). The chemical name of the test article is 8-[(4-amino-1-methylbutyl)amino]-5-(1-hexyloxy)-6-methoxy-4-methylquinoline DL-tartrate and the

mole fraction of the base is 0.71. It was stored at -20 to -15°C and ambient humidity in the freezer, and was protected from light (the container was wrapped in aluminum foil).

3.2 Animals

Thirty-six female New Zealand White (Pasteurella Free) rabbits were obtained from HRP, Inc., Denver, Pennsylvania on June 28, 1994. The animals were ~7 months old upon arrival at the UIC AAALAC-accredited animal facility (date of birth 11/27/93). Each animal was given an ear tag number by the supplier, and a separate study-unique number (ear-tag) upon arrival. This number appeared on a cage card visible on the front of each cage. The cage card additionally contained the study number, test article identification, treatment group number, and dose level. Cage cards were color-coded as a function of treatment group. Animals were singly housed in stainless steel cages in a temperature (61-69°F) and humidity (approx. 30-70 %) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 0.32 $m^2$ area and 38 cm height, was adequate to house rabbits at the upper weight range as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23. All animals were routinely transferred to clean cages every other week with weekly pan changes.

The animals were fasted on the day of arrival. They received approximately 25 g of Purina High Fiber Certified Rabbit Chow #5325 (PMI Feeds, Inc., St. Louis, MO) on the second day, which was gradually increased over a few days to approximately 100-130 g/day. This regimen was recommended by the animal supplier (HRP, Inc.) to reduce the incidence of intestinal problems. On the days of measured food consumption, an exact amount of 130 g was provided. Tap water from an automatic watering system in which the room distribution lines were flushed daily was provided *ad libitum* from arrival until termination. The water was not treated with additional chlorine or HCl. There are no known contaminants in the feed or water which were expected to influence the study. The results of the most current comprehensive chemical analyses of Chicago water performed by the City of Chicago are documented in files maintained by Quality Assurance.

3.3 Experimental Design

Six non-pregnant female rabbits were used to conduct a preliminary dose range-finding test. Two non-pregnant animals/dose (3 dose levels) were dosed with the test article for 13 days. Doses were 0.5, 2 and 6 mg base/kg/day (with a potential of escalation to elicit toxicity). The doses selected were based on the dose range-finding developmental toxicity study in rats (UIC/TRL Study No. 143) and were discussed with the Sponsor. Clinical signs were observed and recorded once daily. Body weights and food consumption were collected on days -2/-1, 0, 4, 7, 10, and 13.

For the subsequent dose range-finding developmental toxicity (Segment II) study in pregnant animals, animals were mated on two consecutive days at the supplier's facility. The day of mating was considered gestation day 0 (GD0). The body weights on GD0 were obtained by the supplier after balance standardization. Of the 36 presumed pregnant rabbits which were received, 18 were at GD2 and the other 18 were at GD3 upon arrival at the animal facility. All animals were quarantined at least for 3 days before initiation

of dosing (GD6). All animals were examined daily during the quarantine period, and were approved for use by the Clinical Veterinarian prior to being placed on test. Thirty animals (fifteen animals from each gestation day 0 subset) were randomized into the following six groups on the basis of body weight to result in 5 animals/group (dose levels chosen were based on the results of the above-mentioned preliminary dose range-finding test):

| Group No. | Dose Level (mg base/kg/day) | Number of Females* |
|---|---|---|
| 1 | 0 | 5 |
| 2 | 0.5 | 5 |
| 3 | 1 | 5 |
| 4 | 2.5 | 5 |
| 5 | 6 | 5 |
| 6 | 14 | 5 |

* Presumed Pregnant

The test article was administered by gavage once daily during gestation days 6 through 18. The dosing suspensions were administered at a dosing volume of 1 ml/kg. A stock test article suspension was prepared weekly by suspending the appropriate quantity of the test article in the vehicle (aqueous 1% Methylcellulose/0.2% Tween 80). Daily dosage formulations were prepared by diluting the stock to the appropriate concentration(s). The stock and dosing suspensions were kept at 0-4°C. Since this study was non-GLP compliant, analytical chemistry analyses were not performed on the dosage formulations. Data from previous WR242511 toxicity studies (UIC/TRL Nos. 106 and 107) showed that the stock formulation and diluted dosing suspensions were stable for at least two weeks and two days, respectively. In addition, several dosing suspensions in one of those studies demonstrated homogeneity, i.e. coefficient of variation between top, middle and bottom was less than 4% (UIC/TRL Study No. 107).

Non-fasted body weights were recorded on GD0 (by the supplier), GD4 (for randomization), and on GD6 - 18, 24 and 29. Food consumption for all animals was measured during the following 24 hr intervals: GD7/8, 9/10, 11/12, 14/15, 17/18, 23/24 and 28/29. Clinical signs were observed and recorded approximately 1 - 2 hours post-dosing on the days of dosing and each morning following the completion of the dosing period. Animals were also observed for moribundity/mortality immediately prior to dosing and in the afternoon, and in the afternoon after dosing ceased.

On GD29, all rabbits were killed in random order by intravenous injection of sodium pentobarbital (50 mg/kg) via the marginal ear vein. The abdominal and thoracic cavities were opened by a ventral midline incision. The uterus was examined and weighed. In gravid animals, the number of *corpora lutea* on each ovary was recorded and the ovaries were discarded after evaluation. The viability of the fetuses were checked *in utero*. A viable fetus was defined as one which responds to stimuli. A non-viable fetus was defined as a term fetus which does not respond to stimuli *in utero* or is not breathing. The number and location of fetuses, early resorption(s), late resorption (s) and the total

number of implantation sites and their uterine distribution were documented using the following procedure. All implantation sites, including resorptions, were numbered in consecutive fashion beginning with the left distal uterine horn, noting the position of the cervix and continuing from the proximal to the distal right uterine horn. An early resorption was defined as one in which it was not grossly evident that organogenesis has occurred. A late resorption was defined as one in which it was grossly evident that organogenesis had occurred. A fetus with evident autolysis was considered a late resorption. Following the cesarean section examination, the carcass of each dam was discarded.

Fetuses were weighed, sexed, and euthanized by sodium pentobarbital (40%), ~ 0.3 ml/fetus I.P., and examined for gross external alterations. One 2.5 mg base/kg/day non-viable fetus was preserved in Bouin's solution, but was not further evaluated. All other fetuses were discarded.

The uterus from a female that appeared nongravid was opened and placed in 0.5% ammonium sulfide solution for at least 10 minutes for detection of possible implantation sites. If implantation sites were detected, ovaries were evaluated as previously mentioned.

3.4 Statistical Analyses:

Maternal body weights, weight gains, uterine absolute and relative weight (% body weight), and fetal body weight were analyzed by one-way analysis of variance. If a significant F ratio was obtained ($p \leq 0.05$), Dunnett's test was used for pairwise comparisons to the control group.

The food consumption data, the numbers of resorptions, nonviable fetuses, viable fetuses, corpora lutea (C.L.), implantations, preimplantation loss* and postimplantation loss** were compared using the Kruskal-Wallis test. If a significant effect was seen ($p \leq 0.05$), the Mann-Whitney U test was used for pairwise comparisons to the control group.

Calculations were as follows:

*Pre-implantation loss % = [(#*Corpora lutea* - # Implants)/ # *Corpora lutea*] x 100
**Post-Implantation loss % = [(#Implants - # Viable fetuses)/ #Implants] x 100
Total loss/litter % = [(#*Corpora lutea* - # Viable fetuses)/ # *Corpora lutea*] x 100

## 4. RESULTS

### 4.1 Preliminary Range-Finding Study in Non-Pregnant Rabbits

Data from the preliminary study are contained in Appendix 3.

In the preliminary range-finding study, the doses (0.5, 2.0 and 6 mg base/kg/day) were given by gavage for 13 days to two non-pregnant females/dose. The mid dose was escalated to 12 mg base/kg/day after 6 days of dosing and then to 24 mg base/kg/day after another 2 days of dosing. Weight loss was observed by day 10, and one animal at this

dose was found dead on day 12. Food consumption was decreased by day 12 at the escalated dose. On day 13, all animals were discarded from the study. Based on these results and a previous dose range-finding developmental toxicity study in rats (UIC/TRL Study No. 143), 0.5 - 14 mg base/kg/day were selected for the main dose range-finding study.

4.2 Mortality/Clinical Observations

The summary of clinical signs of toxicity is in Table 2. Individual signs are in Appendix 1.

Ten animals died in the main study and one was sacrificed moribund. Decreased activity was seen in one female at 6 mg base/kg/day on the day before it was found dead. All animals in the 14 mg base/kg/day dose were dead by GD8. By GD12, all animals in the 6 mg base/kg/day dose were also dead. One animal at the 2.5 mg base/kg/day dose was sacrificed moribund on GD7 due to a non-test article-related effect (i.e. dislocation of the hip). Apart from a decrease in the activity of a female in the 6 mg base/kg/day dose one day prior to death, no other toxicological manifestations were observed in any animal.

One 6 mg base/kg/day animal may have accidently died. Upon returning the animal to its cage after dosing, it unexpectedly jumped and landed on the floor. This animal showed signs of aspiration and asphyxia. It is unclear if the cause of death was or was not test article-related, however, all other animals in this group died as a direct effect of drug toxicity.

4.3 Maternal Body Weights

The summaries of maternal body weights and weight gains are in Tables 3 and 4, respectively. Individual data are included in Appendix 1.

Animals in the 6 mg base/kg/day dose showed a biologically overt decrease in weight by GD8 through GD12, at which time they all had died. At the 2.5 mg base/kg/day dose, one animal showed marginal weight loss. No significant changes in mean body weights were observed in the other surviving dose levels.

4.4 Food Consumption

The summary of mean daily food consumption is in Table 5. Individual food consumption data are shown in Appendix 1.

A significant decrease in food consumption in the 6 mg base/kg/day dose was observed around GD10 (n=3). A biologically marginal decrease in food consumption was also observed at 2.5 mg base/kg/day. This decrease was mainly observed around GD15 and GD18 (i.e. towards the end of dosing).

4.5 Cesarean-Section Observations

The summary of maternal cesarean section data is in Table 6. Individual data are included in Appendix 1.

Apart from one non-viable fetus at 2.5 mg base/kg/day, WR242511 did not affect fetal viability or the rate of resorptions in surviving animals. In surviving dose levels, the numbers of *corpora lutea*, early and late resorptions, number of implantations, calculated pre- or post-implantation losses, or total loss/litter were unaffected by drug treatment. Significant increases in pre-implantation loss % at the 6 and 14 mg base/kg/day doses was expected with 100% total loss due to early maternal mortality. Of the 30 study animals, one animal in the 1 mg base/kg/day dose, one animal in the 2.5 mg base/kg/day dose, and two animals in the 14 mg base/kg/day dose were not pregnant.

4.6 Fetal Observations

The summary of fetal observations is in Table 7. The summary of fetal body weights is in Table 8. Individual data are included in Appendix 2.

At 2.5 mg base/kg/day, one fetus was non-viable, and biologically significant decreases in fetal body weights were observed in both sexes. This decrease was also statistically significant in female fetuses. In the 1 mg base/kg/day dose, mean body weights of female fetuses were also biologically decreased. These biologically significant decreases in fetal body weights were not associated with an overt decrease in maternal body weights which indicated a potential for direct developmental toxicity. No other external abnormalities or variations were observed in any other fetuses in any dose group.

## 5. DISCUSSION/CONCLUSION

This study evaluated limited developmental toxicity data for WR242511 Tartrate in New Zealand White (Pasteurella Free) pregnant rabbits when administered by gavage during gestation days 6-18. Doses were 0, 0.5, 1, 2.5, 6 and 14 mg base/kg/day. The results of this study will be used to aid in the selection of dose levels for a developmental toxicity (Segment II) study in this species, and are summarized in Table 1.

Maternal toxic manifestations included the fatalities of all animals at 14 mg base/kg/day by GD8 and all animals at 6 mg base/kg/day by GD12. In the 6 mg base/kg/day dose, activity was decreased in one animal the day prior to death. A marginal lack in weight gain and decrease in food consumption were observed in at least one of the surviving pregnant females in the 2.5 mg base/kg/day dose. Fetal toxicity at 2.5 mg base/kg/day was seen as significant decreases in fetal body weights. The 2.5 mg base/kg/day dose was considered at or near the low observable adverse effect level for maternal toxicity and the 1 mg base/kg/day dose was considered at or near the low observable adverse effect level for developmental toxicity.

The results of this study and a previous dose range-finding developmental toxicity study in rats (UIC/TRL No. 143) suggested direct developmental toxicity of WR242511 tartrate, and a higher sensitivity in rabbits than rats. In addition, it was evident in rats and rabbits that there is an increased sensitivity of female fetuses to the test article in comparison to the males. However, these results will need to be verified in definitive developmental toxicity (Segment II) studies. The high dose for the definitive developmental toxicity study in rabbits should not exceed 3.5 mg base/kg/day to produce enough surviving females at the high dose to assess toxicity. Accordingly, 0.5, 1.3 and 3.5 mg base/kg/day are suggested as doses for the definitive developmental toxicity (segment II) study in rabbits.

## 6. PERSONNEL

| | |
|---|---|
| Study Director | Barry S. Levine, D.Sc., D.A.B.T. |
| Reproductive Toxicologist | Ashraf F. Youssef, M.D., Ph.D. |
| Reproductive Scientist | Roberto A. Matamoros, D.V.M., Ph.D. |
| Clinical Veterinarian | James Artwohl, D.V.M., M.S., D.A.C.L.A.M. |
| Veterinarian Support | Documented in raw data |
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Report preparation was assisted by Dr. Ashraf Youssef, Ms. Soudabeh Soura and Ms. Rae-Jean Ballentine.

## 7. ARCHIVES

All raw data, documentation, specimens, test article reserves, and the final report are archived at the University of Illinois at Chicago, Toxicology Research Laboratory, Department of Pharmacology, 1940 W. Taylor St., Chicago, IL 60612.

Table 1

## DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

### Summary of Toxic Responses

| Dose Level (mg base/kg/day) | 0.0 | 0.5 | 1.0 | 2.5 | 6.0 | 14.0 |
|---|---|---|---|---|---|---|
| Number of Litters Pregnant (Non-pregnant) | 5(0) | 5(0) | 4(1) | 4(1) | 5[a] (0) | 3[a] (2) |
| Mortality (number of animals) | - | - | - | SM(1) | FD (4)<br>AD (1) | FD (5) |
| Clinical Signs (number of animals) | - | - | - | - | DA (1) | - |
| Decrease in Maternal Body Weight Gain | - | - | - | - | +[b] | NA |
| Decrease in Daily Mean Food Consumption | - | - | - | (?) | +[c] | NA |
| Decrease in Fetal Body Weight (♂/♀) | -/- | -/- | -/+(?) | +(?)/+[d] | NA | NA |
| CONCLUSIONS | Maternal toxic manifestations included the fatalities of all animals at 14 mg base/kg/day by GD8 and all animals at 6 mg base/kg/day by GD12. In the 6 mg base/kg/day dose, activity was decreased in one animal the day prior to death. A marginal lack in weight gain and decrease in food consumption were observed at least in one of the surviving pregnant females in the 2.5 mg base/kg/day dose. Fetal toxicity was seen in 2.5 mg base/kg/day as significant decreases in fetal body weights. The 2.5 mg base/kg/day dose was considered at or near the low observable adverse effect level for maternal toxicity and the 1 mg base/kg/day dose was considered at or near the low observable adverse effect level for developmental toxicity. The results of this study and a previous dose range-finding developmental toxicity study in rats (UIC/TRL No. 143) suggested direct developmental toxicity of WR242511 tartrate, and a higher sensitivity in rabbits than rats. In addition, it was evident in rats and rabbits that there is an increased sensitivity of female fetuses to the test article in comparison to the males. The high dose for the definitive developmental toxicity study in rabbits should not exceed 3.5 mg base/kg/day to produce enough surviving females at the high dose to assess toxicity. Accordingly, 0.5, 1.3 and 3.5 mg base/kg/day are suggested as doses for the definitive developmental toxicity (segment II) study in rabbits. | | | | | |

AD = Accidental death (due to aspiration and trauma)
DA = Decreased Activity
SM = Sacrificed Moribund on GD7 (dislocated hip)
FD = Found Dead on GD12
[a]Litter data collection was not possible due to autolytic changes
[b]Evaluated through day 12
[c]Significantly different ($p < 0.05$) from the control only on GD10 by Kruskal-Wallis/ Mann-Whitney U Test
[d]Significantly different ($p < 0.05$) from the control by ANOVA/Dunnett's Test

- = Absent
+ = Present
(?) = Possible Effect
NA = Not applicable

Table 2
DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**SUMMARY OF CLINICAL SIGNS**

STUDY: 137 SEX: FEMALE

| DOSE: (mg base/kg/day) | 0 | 0.5 | 1 | 2.5 | 6 | 14 |
|---|---|---|---|---|---|---|
| GROUP: | 1-F | 2-F | 3-F | 4-F | 5-F | 6-F |
| Accidental Death | 0 | 0 | 0 | 0 | 1 | 0 |
| Scheduled Sacrifice | 5 | 5 | 4 | 4 | 0 | 0 |
| Animal Found Dead | 0 | 0 | 0 | 0 | 4 | 5 |
| Sacrificed Moribund | 0 | 0 | 0 | 1 | 0 | 0 |
| Decreased Activity | 0 | 0 | 0 | 0 | 1 | 0 |
| Total Number of Animals | 5 | 5 | 5 | 5 | 5 | 5 |

Table 3

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 137 SEX: FEMALE

| PERIOD | DOSE: / GROUP: | 0 1-F | 0.5 2-F | 1 3-F | 2.5 4-F | 6 5-F | 14 6-F (mg base/kg/day) |
|---|---|---|---|---|---|---|---|
| DAY 0 | MEAN | 3.79 | 3.92 | 3.92 | 3.93 | 3.86 | 3.82 |
| | S.D. | 0.287 | 0.181 | 0.268 | 0.226 | 0.176 | 0.315 |
| | N | 5 | 5 | 4 | 4 | 5 | 3 |
| DAY 4 | MEAN | 3.87 | 3.93 | 3.92 | 4.02 | 3.86 | 3.83 |
| | S.D. | 0.225 | 0.255 | 0.268 | 0.314 | 0.182 | 0.271 |
| | N | 5 | 5 | 4 | 4 | 5 | 3 |
| DAY 6 | MEAN | 3.81 | 3.88 | 3.85 | 3.88 | 3.80 | 3.77 |
| | S.D. | 0.263 | 0.254 | 0.278 | 0.255 | 0.161 | 0.339 |
| | N | 5 | 5 | 4 | 4 | 5 | 3 |
| DAY 7 | MEAN | 3.84 | 3.88 | 3.91 | 3.84 | 3.80 | 3.78 |
| | S.D. | 0.256 | 0.238 | 0.290 | 0.255 | 0.153 | 0.380 |
| | N | 5 | 5 | 4 | 4 | 5 | 3 |
| DAY 8 | MEAN | 3.86 | 3.87 | 3.86 | 3.85 | 3.76 | -- |
| | S.D. | 0.215 | 0.237 | 0.262 | 0.221 | 0.190 | -- |
| | N | 5 | 5 | 4 | 4 | 5 | 0 |
| DAY 9 | MEAN | 3.86 | 3.89 | 3.87 | 3.90 | 3.81 | -- |
| | S.D. | 0.264 | 0.241 | 0.274 | 0.224 | 0.193 | -- |
| | N | 5 | 5 | 4 | 4 | 3 | 0 |
| DAY 10 | MEAN | 3.82 | 3.90 | 3.87 | 3.92 | 3.71 | -- |
| | S.D. | 0.274 | 0.224 | 0.291 | 0.234 | 0.231 | -- |
| | N | 5 | 5 | 4 | 4 | 3 | 0 |
| DAY 11 | MEAN | 3.85 | 3.90 | 3.86 | 3.94 | 3.77 | -- |
| | S.D. | 0.285 | 0.203 | 0.292 | 0.254 | 0.035 | -- |
| | N | 5 | 5 | 4 | 4 | 2 | 0 |
| DAY 12 | MEAN | 3.86 | 3.94 | 3.86 | 3.95 | 3.61 | -- |
| | S.D. | 0.286 | 0.212 | 0.311 | 0.277 | 0.000 | -- |
| | N | 5 | 5 | 4 | 4 | 1 | 0 |
| DAY 13 | MEAN | 3.89 | 3.93 | 3.90 | 3.96 | -- | -- |
| | S.D. | 0.294 | 0.217 | 0.309 | 0.287 | -- | -- |
| | N | 5 | 5 | 4 | 4 | 0 | 0 |

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

-- = Data Unavailable

Table 3 (contd.)

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**SUMMARY OF BODY WEIGHTS** (Kilograms)

STUDY: 137 SEX: FEMALE

| PERIOD | DOSE: / GROUP: | 0 1-F | 0.5 2-F | 1 3-F | 2.5 4-F | 6 5-F | 14 6-F | (mg base/kg/day) |
|---|---|---|---|---|---|---|---|---|
| DAY 14 | MEAN | 3.92 | 3.98 | 3.95 | 3.98 | -- | -- | |
| | S.D. | 0.305 | 0.227 | 0.310 | 0.303 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 15 | MEAN | 3.92 | 3.95 | 3.98 | 4.03 | -- | -- | |
| | S.D. | 0.313 | 0.226 | 0.312 | 0.345 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 16 | MEAN | 3.92 | 3.95 | 4.01 | 3.99 | -- | -- | |
| | S.D. | 0.324 | 0.231 | 0.284 | 0.400 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 17 | MEAN | 3.93 | 3.95 | 4.00 | 3.97 | -- | -- | |
| | S.D. | 0.335 | 0.217 | 0.314 | 0.388 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 18 | MEAN | 3.94 | 3.92 | 4.01 | 3.97 | -- | -- | |
| | S.D. | 0.335 | 0.206 | 0.296 | 0.374 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 29 | MEAN | 4.04 | 4.02 | 4.14 | 3.99 | -- | -- | |
| | S.D. | 0.307 | 0.341 | 0.325 | 0.390 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

-- = Data Unavailable

Table 4
DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**SUMMARY OF WEIGHT GAINS** (Kilograms)

STUDY: 137 SEX: FEMALE

| PERIOD[a] | DOSE: GROUP: | 0 1-F | 0.5 2-F | 1 3-F | 2.5 4-F | 6 5-F | 14 6-F | (mg base/kg/day) |
|---|---|---|---|---|---|---|---|---|
| DAY 7[b] | MEAN | 0.03 | 0.00 | 0.06 | -0.04 | 0.00 | 0.01 | |
| | S.D. | 0.095 | 0.046 | 0.029 | 0.115 | 0.025 | 0.042 | |
| | N | 5 | 5 | 4 | 4 | 5 | 3 | |
| DAY 8 | MEAN | 0.01 | 0.00 | -0.05 | 0.01 | -0.05 | -- | |
| | S.D. | 0.067 | 0.018 | 0.061 | 0.076 | 0.047 | -- | |
| | N | 5 | 5 | 4 | 4 | 5 | 0 | |
| DAY 9 | MEAN | 0.01 | 0.01 | 0.01 | 0.06 | -0.02 | -- | |
| | S.D. | 0.085 | 0.025 | 0.029 | 0.031 | 0.050 | -- | |
| | N | 5 | 5 | 4 | 4 | 3 | 0 | |
| DAY 10 | MEAN | -0.05 | 0.01 | 0.00 | 0.02 | -0.10 | -- | |
| | S.D. | 0.077 | 0.023 | 0.029 | 0.030 | 0.055 | -- | |
| | N | 5 | 5 | 4 | 4 | 3 | 0 | |
| DAY 11 | MEAN | 0.03 | 0.00 | -0.02 | 0.02 | -0.08 | -- | |
| | S.D. | 0.048 | 0.037 | 0.041 | 0.047 | 0.014 | -- | |
| | N | 5 | 5 | 4 | 4 | 2 | 0 | |
| DAY 12 | MEAN | 0.01 | 0.04 | 0.01 | 0.01 | -0.13* | -- | |
| | S.D. | 0.036 | 0.019 | 0.058 | 0.049 | 0.000 | -- | |
| | N | 5 | 5 | 4 | 4 | 1 | 0 | |
| DAY 13 | MEAN | 0.03 | -0.01 | 0.04 | 0.00 | -- | -- | |
| | S.D. | 0.030 | 0.034 | 0.014 | 0.013 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 14 | MEAN | 0.03 | 0.05 | 0.04 | 0.02 | -- | -- | |
| | S.D. | 0.025 | 0.042 | 0.022 | 0.054 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 15 | MEAN | 0.01 | -0.03 | 0.04 | 0.05 | -- | -- | |
| | S.D. | 0.021 | 0.040 | 0.010 | 0.088 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 16 | MEAN | -0.01 | 0.00 | 0.03 | -0.04 | -- | -- | |
| | S.D. | 0.035 | 0.075 | 0.118 | 0.108 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

-- = Data Unavailable

[a] Successive periods

[b] Baseline is Day 6

Table 4 (contd.)
DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**SUMMARY OF WEIGHT GAINS** (Kilograms)

STUDY: 137 SEX: FEMALE

| PERIOD [a] | DOSE: GROUP: | 0 1-F | 0.5 2-F | 1 3-F | 2.5 4-F | 6 5-F | 14 6-F | (mg base/kg/day) |
|---|---|---|---|---|---|---|---|---|
| DAY 17 | MEAN | 0.02 | 0.00 | -0.01 | -0.02 | -- | -- | |
| | S.D. | 0.021 | 0.030 | 0.116 | 0.022 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 18 | MEAN | 0.01 | -0.03 | 0.01 | 0.00 | -- | -- | |
| | S.D. | 0.040 | 0.062 | 0.018 | 0.022 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| DAY 29 | MEAN | 0.10 | 0.10 | 0.13 | 0.02 | -- | -- | |
| | S.D. | 0.055 | 0.162 | 0.045 | 0.158 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |
| TOTAL GAIN | MEAN | 0.23 | 0.14 | 0.29 | 0.11 | -- | -- | |
| | S.D. | 0.067 | 0.189 | 0.054 | 0.155 | -- | -- | |
| | N | 5 | 5 | 4 | 4 | 0 | 0 | |

* P less than .05 Analysis of Variance using DUNNETT'S Procedure

-- = Data Unavailable

a = Successive periods

Table 5

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 137 SEX: FEMALE

| PERIOD | DOSE: (mg base/kg/day) / GROUP: | 0<br>1-F | 0.5<br>2-F | 1<br>3-F | 2.5<br>4-F | 6<br>5-F | 14<br>6-F |
|---|---|---|---|---|---|---|---|
| DAY 8 | INTAKE (g) | 130 | 128 | 115 | 118 | 106 | 0 |
| | S.D. | 0.0 | 3.5 | 26.0 | 19.0 | 27.5 | 0.0 |
| | N | 5 | 5 | 4 | 4 | 5 | 1 |
| DAY 10 | INTAKE (g) | 129 | 114 | 92 | 130 | 22 * | -- |
| | S.D. | 1.8 | 26.5 | 53.7 | 0.0 | 21.0 | 0.0 |
| | N | 5 | 5 | 4 | 4 | 3 | 0 |
| DAY 12 | INTAKE (g) | 119 | 120 | 109 | 116 | 0 | -- |
| | S.D. | 24.6 | 13.3 | 39.2 | 16.9 | 0.0 | 0.0 |
| | N | 5 | 5 | 4 | 4 | 1 | 0 |
| DAY 15 | INTAKE (g) | 119 | 92 | 104 | 74 | -- | -- |
| | S.D. | 16.1 | 54.4 | 49.7 | 66.0 | 0.0 | 0.0 |
| | N | 5 | 5 | 4 | 4 | 0 | 0 |
| DAY 18 | INTAKE (g) | 130 | 106 | 123 | 88 | -- | -- |
| | S.D. | 0.0 | 36.3 | 14.0 | 49.9 | 0.0 | 0.0 |
| | N | 5 | 5 | 4 | 4 | 0 | 0 |
| DAY 24 | INTAKE (g) | 130 | 109 | 130 | 119 | -- | -- |
| | S.D. | 0.0 | 32.0 | 0.0 | 21.5 | 0.0 | 0.0 |
| | N | 5 | 5 | 4 | 4 | 0 | 0 |
| DAY 29 | INTAKE (g) | 112 | 103 | 122 | 98 | -- | -- |
| | S.D. | 28.6 | 27.6 | 8.4 | 43.9 | 0.0 | 0.0 |
| | N | 5 | 5 | 4 | 4 | 0 | 0 |

-- = Data Unavailable

Statistical Analysis by Kruskal-Wallis test and Mann-Whitney U test

* P less than .05

Table 6

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS

Summary of Maternal Cesarean Section Data
(Mean ± S.D.)

| Dose Level (mg base/kg/day) | 0 | 0.5 | 1 | 2.5 | 6 | 14 |
|---|---|---|---|---|---|---|
| Total Number of Females/Group | 5 | 5 | 5 | 5 | 5 | 5 |
| Total Number of Surviving Females | 5 | 5 | 5 | 4 | 0 | 0 |
| Total Number of Pregnant Females | 5 | 5 | 4 | 4 | 5 | 3 |
| Uterine Weight (% Body Weight) | 10.4 ± 2.4 | 12.7 ± 2.4 | 10.2 ± 2.1 | 10.0 ± 2.2 | 0 | 0 |
| Implantation Sites | 7.4 ± 1.2 | 9.0 ± 2.0 | 8.0 ± 2.4 | 7.8 ± 1.6 | 8.8 ± 1.9 | 10.3 ± 6.0 |
| Corpora Lutea | 8.0 ± 1.1 | 11.6 ± 2.7* | 9.5 ± 0.9 | 8.8 ± 0.8 | 10.2 ± 1.0* | 10.3 ± 1.9 |
| Early Resorptions | 0.6 ± 0.8 | 0.2 ± 0.4 | 0.3 ± 0.4 | 0.3 ± 0.4 | 2.0 ± 4.0* | 3.7 ± 1.7* |
| Late Resorptions | 0.0 | 0.0 | 0.3 ± 0.4 | 0.0 | 3.0 ± 3.7 | 0.0 |
| Viable Fetuses | 6.8 ± 1.2 | 8.8 ± 2.0 | 7.5 ± 2.1 | 7.3 ± 1.5 | [d] | [d] |
| Non-Viable Fetuses | 0.0 | 0.0 | 0.0 | 0.3 ± 0.4 | [d] | [d] |
| Pre-Implantation Loss %[a] | 7.8 ± 6.7 | 21.7 ± 11.8 | 15.0 ± 26.0 | 11.3 ± 19.1 | 14.2 ± 13.5 | 3.4 ± 53.3 |
| Post-Implantation Loss %[b] | 7.5 ± 10.0 | 2.2 ± 4.4 | 5.0 ± 5.0 | 5.6 ± 9.6 | [d] | [d] |
| Total Loss / Litter %[c] | 14.7 ± 10.8 | 23.7 ± 10.4 | 20.0 ± 23.5 | 16.8 ± 18.2 | 100.0 ± 0.0 | 100.0 ± 0.0 |

Statistical Analysis: Uterine Weight by ANOVA/Dunnett's Test, all other data by Kruskal-Wallis/Mann-Whitney U Test.

[a]Pre Implantation Loss % = [(# Corpora Lutea - # Implants)/ # Corpora Lutea] x 100
[b]Post Implantation Loss % = [(# Implants - # Viable Fetuses)/ # Implants] x 100
[c]Total Loss/Litter = [(# Corpora Lutea - # Viable Fetuses)/ # Corpora Lutea] x 100
[d]Due to early maternal fatality, these parameters could not be evaluated.
*Statistically Significant ($p \leq 0.05$)

Table 7

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS

Summary of Fetal Observations

| Dose Level (mg base/kg/day) | | 0 | 0.5 | 1 | 2.5 | 6[c] | 14[c] |
|---|---|---|---|---|---|---|---|
| Total # of Fetuses (# of Litters)[a] | | 34 (5) | 44 (5) | 30 (5) | 29 (4) | NA | NA |
| Sex Distribution: | Males | 19 | 18 | 16 | 15 | NA | NA |
| | Females | 15 | 26 | 14 | 14 | NA | NA |
| Sex Ratio: | Males/Females % | 56/44 | 41/59 | 53/47 | 52/48 | NA | NA |
| Body Weight (g): (Mean ± S.D.) | Males | 43.67 ± 4.949 | 41.32 ± 7.043 | 42.55 ± 6.046 | 38.59 ± 3.880 | NA | NA |
| | Females | 43.64 ± 4.539 | 42.50 ± 5.759 | 38.94 ± 6.534 | 36.14 ± 4.868* | NA | NA |
| Number of Normal Fetuses (%) | | 34 (100) | 44 (100) | 30 (100) | 28 (97) | NA | NA |
| Number of Fetuses with Variations[b] | | 0 | 0 | 0 | 1 | NA | NA |

[a]All fetuses except one (2.5 mg base/kg/day dose group) were viable
[b]Hematoma or Petechial Hemorrhage (normal variations)
[c]Animals died early
*Statistically Significant ($p \leq 0.05$) by ANOVA/Dunnett's Test
NA = Not Applicable

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# APPENDIX 1

## INDIVIDUAL MATERNAL DATA

- Individual Observations
- Individual Body Weights
- Individual Weight Gain
- Individual Daily Food Consumption
- Individual Uterine Weights
- Individual Maternal Cesarean Section Data

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

**INDIVIDUAL CLINICAL SIGNS**

STUDY: 137 GROUP: 1-F SEX: FEMALE
DAY 6-DAY 29 DOSE: 0 (mg base/kg/day)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 151 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 152 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 153 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 154 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 155 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |

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DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

**INDIVIDUAL CLINICAL SIGNS**

STUDY: 137 GROUP: 2-F SEX: FEMALE
DAY 6-DAY 29 DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 156 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 157 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 158 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 159 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 160 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |

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DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

**INDIVIDUAL CLINICAL SIGNS**

STUDY: 137 GROUP: 3-F SEX: FEMALE
DAY 6-DAY 29 DOSE: 1 (mg base/kg/day)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 161 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 162 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 163 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 165 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

## INDIVIDUAL CLINICAL SIGNS

STUDY: 137 GROUP: 4-F SEX: FEMALE
DAY 6-DAY 29 DOSE: 2.5 (mg base/kg/day)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 166 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 167 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 168 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |
| 169 | Sacrificed Moribund | | | DAY 7 |
| 170 | Normal | | | DAY 6-DAY 28 |
| | Scheduled Sacrifice | | | DAY 29 |

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DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

**INDIVIDUAL CLINICAL SIGNS**

STUDY: 137 GROUP: 5-F SEX: FEMALE
DAY 6-DAY 29 DOSE: 6 (mg base/kg/day)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 171 | Decreased Activity | | | DAY 10 |
| | Animal Found Dead | | | DAY 11 |
| | Normal | | | DAY 6-DAY 9 |
| 172 | Animal Found Dead | | | DAY 9 |
| | Normal | | | DAY 6-DAY 8 |
| 173 | Animal Found Dead | | | DAY 9 |
| | Normal | | | DAY 6-DAY 8 |
| 174 | Accidental Death | | | DAY 12 |
| | Normal | | | DAY 6-DAY 11 |
| 175 | Animal Found Dead | | | DAY 12 |
| | Normal | | | DAY 6-DAY 11 |

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

**INDIVIDUAL CLINICAL SIGNS**

STUDY: 137 GROUP: 6-F SEX: FEMALE
DAY 6-DAY 29 DOSE: 14 (mg base/kg/day)

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 176 | Animal Found Dead | | | DAY 8 |
| | Normal | | | DAY 6-DAY 7 |
| 177 | Animal Found Dead | | | DAY 8 |
| | Normal | | | DAY 6-DAY 7 |
| 178 | Animal Found Dead | | | DAY 8 |
| | Normal | | | DAY 6-DAY 7 |
| 179 | Animal Found Dead | | | DAY 8 |
| | Normal | | | DAY 6-DAY 7 |
| 180 | Animal Found Dead | | | DAY 8 |
| | Normal | | | DAY 6-DAY 7 |

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 137 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

| ANIMAL # | DAY 0 | DAY 4 | DAY 6 | DAY 7 | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 151 | 3.47 | 3.65 | 3.59 | 3.53 | 3.54 | 3.57 | 3.59 | 3.63 | 3.65 | 3.63 | 3.67 | 3.67 |
| 152 | 3.50 | 3.63 | 3.50 | 3.67 | 3.77 | 3.66 | 3.50 | 3.48 | 3.51 | 3.56 | 3.57 | 3.56 |
| 153 | 4.10 | 4.08 | 4.06 | 4.04 | 3.99 | 4.02 | 4.04 | 4.03 | 4.07 | 4.12 | 4.16 | 4.20 |
| 154 | 3.99 | 4.10 | 4.07 | 4.15 | 4.10 | 4.22 | 4.13 | 4.17 | 4.20 | 4.23 | 4.28 | 4.27 |
| 155 | 3.87 | 3.88 | 3.85 | 3.82 | 3.88 | 3.85 | 3.82 | 3.92 | 3.87 | 3.92 | 3.91 | 3.92 |
| MEAN | 3.79 | 3.87 | 3.81 | 3.84 | 3.86 | 3.86 | 3.82 | 3.85 | 3.86 | 3.89 | 3.92 | 3.92 |
| S.D. | 0.287 | 0.225 | 0.263 | 0.256 | 0.215 | 0.264 | 0.274 | 0.285 | 0.286 | 0.294 | 0.305 | 0.313 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 137 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

| ANIMAL # | DAY 16 | DAY 17 | DAY 18 | DAY 29 |
|---|---|---|---|---|
| 151 | 3.67 | 3.69 | 3.69 | 3.76 |
| 152 | 3.51 | 3.51 | 3.51 | 3.70 |
| 153 | 4.21 | 4.22 | 4.18 | 4.25 |
| 154 | 4.24 | 4.29 | 4.31 | 4.41 |
| 155 | 3.96 | 3.96 | 4.03 | 4.08 |
| MEAN | 3.92 | 3.93 | 3.94 | 4.04 |
| S.D. | 0.324 | 0.335 | 0.335 | 0.307 |
| N | 5 | 5 | 5 | 5 |

--: Data Unavailable

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# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 137 GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY 0 | DAY 4 | DAY 6 | DAY 7 | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 156 | 3.94 | 3.94 | 3.84 | 3.86 | 3.87 | 3.85 | 3.86 | 3.90 | 3.93 | 3.96 | 4.00 | 4.04 |
| 157 | 3.79 | 3.66 | 3.53 | 3.57 | 3.55 | 3.56 | 3.61 | 3.62 | 3.64 | 3.64 | 3.64 | 3.60 |
| 158 | 3.80 | 3.94 | 3.84 | 3.85 | 3.87 | 3.88 | 3.89 | 3.86 | 3.93 | 3.91 | 4.00 | 3.96 |
| 159 | 3.86 | 3.79 | 3.94 | 3.86 | 3.85 | 3.90 | 3.89 | 3.91 | 3.96 | 3.90 | 4.00 | 3.95 |
| 160 | 4.23 | 4.34 | 4.24 | 4.24 | 4.22 | 4.24 | 4.24 | 4.19 | 4.24 | 4.25 | 4.28 | 4.22 |
| MEAN | 3.92 | 3.93 | 3.88 | 3.88 | 3.87 | 3.89 | 3.90 | 3.90 | 3.94 | 3.93 | 3.98 | 3.95 |
| S.D. | 0.181 | 0.255 | 0.254 | 0.238 | 0.237 | 0.241 | 0.224 | 0.203 | 0.212 | 0.217 | 0.227 | 0.226 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 137 GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY 16 | DAY 17 | DAY 18 | DAY 29 |
|---|---|---|---|---|
| 156 | 3.99 | 4.03 | 4.02 | 4.23 |
| 157 | 3.56 | 3.58 | 3.60 | 3.60 |
| 158 | 3.98 | 3.96 | 3.93 | 3.98 |
| 159 | 4.07 | 4.04 | 3.91 | 3.82 |
| 160 | 4.16 | 4.14 | 4.16 | 4.47 |
| MEAN | 3.95 | 3.95 | 3.92 | 4.02 |
| S.D. | 0.231 | 0.217 | 0.206 | 0.341 |
| N | 5 | 5 | 5 | 5 |

--: Data Unavailable

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 137 GROUP: 3-F SEX: FEMALE
DOSE: 1 (mg base/kg/day)

| ANIMAL # | DAY 0 | DAY 4 | DAY 6 | DAY 7 | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 161 | 3.54 | 3.58 | 3.48 | 3.51 | 3.53 | 3.51 | 3.48 | 3.46 | 3.48 | 3.51 | 3.57 | 3.61 |
| 162 | 4.07 | 4.13 | 4.05 | 4.13 | 4.05 | 4.04 | 4.02 | 4.06 | 4.13 | 4.16 | 4.21 | 4.26 |
| 163 | 3.92 | 3.83 | 3.80 | 3.89 | 3.77 | 3.81 | 3.83 | 3.81 | 3.74 | 3.80 | 3.81 | 3.84 |
| 164 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| 165 | 4.14 | 4.14 | 4.08 | 4.12 | 4.09 | 4.12 | 4.15 | 4.09 | 4.10 | 4.14 | 4.19 | 4.22 |
| MEAN | 3.92 | 3.92 | 3.85 | 3.91 | 3.86 | 3.87 | 3.87 | 3.86 | 3.86 | 3.90 | 3.95 | 3.98 |
| S.D. | 0.268 | 0.268 | 0.278 | 0.290 | 0.262 | 0.274 | 0.291 | 0.292 | 0.311 | 0.309 | 0.310 | 0.312 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 137 GROUP: 3-F SEX: FEMALE
DOSE: 1 (mg base/kg/day)

| ANIMAL # | DAY 16 | DAY 17 | DAY 18 | DAY 29 |
|---|---|---|---|---|
| 161 | 3.60 | 3.62 | 3.65 | 3.72 |
| 162 | 4.19 | 4.28 | 4.28 | 4.40 |
| 163 | 4.04 | 3.86 | 3.88 | 4.04 |
| 164 | -- | -- | -- | -- |
| 165 | 4.21 | 4.23 | 4.22 | 4.39 |
| MEAN | 4.01 | 4.00 | 4.01 | 4.14 |
| S.D. | 0.284 | 0.314 | 0.296 | 0.325 |
| N | 4 | 4 | 4 | 4 |

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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## INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 137 GROUP: 4-F SEX: FEMALE
DOSE: 2.5 (mg base/kg/day)

| ANIMAL # | DAY 0 | DAY 4 | DAY 6 | DAY 7 | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 166 | 4.12 | 4.36 | 4.20 | 4.22 | 4.15 | 4.19 | 4.20 | 4.20 | 4.24 | 4.26 | 4.24 | 4.42 |
| 167 | 3.79 | 3.67 | 3.65 | 3.66 | 3.66 | 3.68 | 3.69 | 3.68 | 3.72 | 3.72 | 3.71 | 3.72 |
| 168 | 4.13 | 4.20 | 3.97 | 3.76 | 3.87 | 3.96 | 4.02 | 4.11 | 4.14 | 4.14 | 4.24 | 4.22 |
| 169 | -- | -- | -- | d | d | d | d | d | d | d | d | d |
| 170 | 3.69 | 3.86 | 3.70 | 3.73 | 3.71 | 3.78 | 3.77 | 3.77 | 3.71 | 3.70 | 3.72 | 3.76 |
| MEAN | 3.93 | 4.02 | 3.88 | 3.84 | 3.85 | 3.90 | 3.92 | 3.94 | 3.95 | 3.96 | 3.98 | 4.03 |
| S.D. | 0.226 | 0.314 | 0.255 | 0.255 | 0.221 | 0.224 | 0.234 | 0.254 | 0.277 | 0.287 | 0.303 | 0.345 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

--: Data Unavailable d: Sacrificed Moribund

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DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 137 GROUP: 4-F SEX: FEMALE
DOSE: 2.5 (mg base/kg/day)

| ANIMAL # | DAY 16 | DAY 17 | DAY 18 | DAY 29 |
|---|---|---|---|---|
| 166 | 4.36 | 4.32 | 4.29 | 4.39 |
| 167 | 3.71 | 3.72 | 3.74 | 3.57 |
| 168 | 4.30 | 4.27 | 4.28 | 4.24 |
| 169 | d | d | d | d |
| 170 | 3.58 | 3.55 | 3.56 | 3.75 |
| MEAN | 3.99 | 3.97 | 3.97 | 3.99 |
| S.D. | 0.400 | 0.388 | 0.374 | 0.390 |
| N | 4 | 4 | 4 | 4 |

--: Data Unavailable d: Sacrificed Moribund

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# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 137 GROUP: 5-F SEX: FEMALE
DOSE: 6 (mg base/kg/day)

| ANIMAL # | DAY 0 | DAY 4 | DAY 6 | DAY 7 | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 171 | 3.84 | 3.86 | 3.68 | 3.70 | 3.67 | 3.60 | 3.45 | c | c | c | c | c |
| 172 | 3.77 | 3.76 | 3.84 | 3.85 | 3.81 | c | c | c | c | c | c | c |
| 173 | 3.63 | 3.61 | 3.59 | 3.59 | 3.47 | c | c | c | c | c | c | c |
| 174 | 4.08 | 4.08 | 3.97 | 3.93 | 3.88 | 3.85 | 3.81 | 3.74 | 3.61 | a | a | a |
| 175 | 3.98 | 3.97 | 3.92 | 3.94 | 3.95 | 3.98 | 3.88 | 3.79 | c | c | c | c |
| MEAN | 3.86 | 3.86 | 3.80 | 3.80 | 3.76 | 3.81 | 3.71 | 3.77 | 3.61 | -- | -- | -- |
| S.D. | 0.176 | 0.182 | 0.161 | 0.153 | 0.190 | 0.193 | 0.231 | 0.035 | -- | -- | -- | -- |
| N | 5 | 5 | 5 | 5 | 5 | 3 | 3 | 2 | 1 | 0 | 0 | 0 |

--: Data Unavailable a: Accidental Death c: Animal Found Dead

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 137 GROUP: 5-F SEX: FEMALE
DOSE: 6 (mg base/kg/day)

| ANIMAL # | DAY 16 | DAY 17 | DAY 18 | DAY 29 |
|---|---|---|---|---|
| 171 | c | c | c | c |
| 172 | c | c | c | c |
| 173 | c | c | c | c |
| 174 | a | a | a | a |
| 175 | c | c | c | c |
| MEAN | -- | -- | -- | -- |
| S.D. | -- | -- | -- | -- |
| N | 0 | 0 | 0 | 0 |

--: Data Unavailable a: Accidental Death c: Animal Found Dead

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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## INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 137 GROUP: 6-F SEX: FEMALE
DOSE: 14 (mg base/kg/day)

| ANIMAL # | DAY 0 | DAY 4 | DAY 6 | DAY 7 | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 176 | 3.56 | 3.64 | 3.46 | 3.44 | c | c | c | c | c | c | c | c |
| 177 | -- | -- | -- | -- | c | c | c | c | c | c | c | c |
| 178 | -- | -- | -- | -- | c | c | c | c | c | c | c | c |
| 179 | 4.17 | 4.14 | 4.13 | 4.19 | c | c | c | c | c | c | c | c |
| 180 | 3.73 | 3.71 | 3.71 | 3.71 | c | c | c | c | c | c | c | c |
| MEAN | 3.82 | 3.83 | 3.77 | 3.78 | -- | -- | -- | -- | -- | -- | -- | -- |
| S.D. | 0.315 | 0.271 | 0.339 | 0.380 | -- | -- | -- | -- | -- | -- | -- | -- |
| N | 3 | 3 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

--: Data Unavailable c: Animal Found Dead

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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**INDIVIDUAL BODY WEIGHTS** (Kilograms)

STUDY: 137 GROUP: 6-F SEX: FEMALE
DOSE: 14 (mg base/kg/day)

| ANIMAL # | DAY 16 | DAY 17 | DAY 18 | DAY 29 |
|---|---|---|---|---|
| 176 | c | c | c | c |
| 177 | c | c | c | c |
| 178 | c | c | c | c |
| 179 | c | c | c | c |
| 180 | c | c | c | c |
| MEAN | -- | -- | -- | -- |
| S.D. | -- | -- | -- | -- |
| N | 0 | 0 | 0 | 0 |

--: Data Unavailable c: Animal Found Dead

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**INDIVIDUAL WEIGHT GAIN** (Kilograms)[a]

STUDY: 137 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

| ANIMAL # | DAY 7[b] | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 | DAY 16 | DAY 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 151 | -0.06 | 0.01 | 0.03 | 0.02 | 0.04 | 0.02 | -0.02 | 0.04 | 0.00 | 0.00 | 0.02 |
| 152 | 0.17 | 0.10 | -0.11 | -0.16 | -0.02 | 0.03 | 0.05 | 0.01 | -0.01 | -0.05 | 0.00 |
| 153 | -0.02 | -0.05 | 0.03 | 0.02 | -0.01 | 0.04 | 0.05 | 0.04 | 0.04 | 0.01 | 0.01 |
| 154 | 0.08 | -0.05 | 0.12 | -0.09 | 0.04 | 0.03 | 0.03 | 0.05 | -0.01 | -0.03 | 0.05 |
| 155 | -0.03 | 0.06 | -0.03 | -0.03 | 0.10 | -0.05 | 0.05 | -0.01 | 0.01 | 0.04 | 0.00 |
| MEAN | 0.03 | 0.01 | 0.01 | -0.05 | 0.03 | 0.01 | 0.03 | 0.03 | 0.01 | -0.01 | 0.02 |
| S.D. | 0.095 | 0.067 | 0.085 | 0.077 | 0.048 | 0.036 | 0.030 | 0.025 | 0.021 | 0.035 | 0.021 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

--: Data Unavailable

[a] Successive periods

[b] Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**INDIVIDUAL WEIGHT GAIN** (Kilograms)[a]

STUDY: 137 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

| ANIMAL # | DAY 18 | DAY 29 | TOTAL GAIN |
|---|---|---|---|
| 151 | 0.00 | 0.07 | 0.17 |
| 152 | 0.00 | 0.19 | 0.20 |
| 153 | -0.04 | 0.07 | 0.19 |
| 154 | 0.02 | 0.10 | 0.34 |
| 155 | 0.07 | 0.05 | 0.23 |
| MEAN | 0.01 | 0.10 | 0.23 |
| S.D. | 0.040 | 0.055 | 0.067 |
| N | 5 | 5 | 5 |

--: Data Unavailable b: Scheduled Sacrifice

[a]Successive periods

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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## INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 137 GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY 7[b] | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 | DAY 16 | DAY 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 156 | 0.02 | 0.01 | -0.02 | 0.01 | 0.04 | 0.03 | 0.03 | 0.04 | 0.04 | -0.05 | 0.04 |
| 157 | 0.04 | -0.02 | 0.01 | 0.05 | 0.01 | 0.02 | 0.00 | 0.00 | -0.04 | -0.04 | 0.02 |
| 158 | 0.01 | 0.02 | 0.01 | 0.01 | -0.03 | 0.07 | -0.02 | 0.09 | -0.04 | 0.02 | -0.02 |
| 159 | -0.08 | -0.01 | 0.05 | -0.01 | 0.02 | 0.05 | -0.06 | 0.10 | -0.05 | 0.12 | -0.03 |
| 160 | 0.00 | -0.02 | 0.02 | 0.00 | -0.05 | 0.05 | 0.01 | 0.03 | -0.06 | -0.06 | -0.02 |
| MEAN | 0.00 | 0.00 | 0.01 | 0.01 | 0.00 | 0.04 | -0.01 | 0.05 | -0.03 | 0.00 | 0.00 |
| S.D. | 0.046 | 0.018 | 0.025 | 0.023 | 0.037 | 0.019 | 0.034 | 0.042 | 0.040 | 0.075 | 0.030 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

--: Data Unavailable

[a] Successive periods

[b] Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**INDIVIDUAL WEIGHT GAIN** (Kilograms)[a]

STUDY: 137 GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY 18 | DAY 29 | TOTAL GAIN |
|---|---|---|---|
| 156 | -0.01 | 0.21 | 0.39 |
| 157 | 0.02 | 0.00 | 0.07 |
| 158 | -0.03 | 0.05 | 0.14 |
| 159 | -0.13 | -0.09 | -0.12 |
| 160 | 0.02 | 0.31 | 0.23 |
| MEAN | -0.03 | 0.10 | 0.14 |
| S.D. | 0.062 | 0.162 | 0.189 |
| N | 5 | 5 | 5 |

--: Data Unavailable b: Scheduled Sacrifice

[a]Successive periods

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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## INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 137 GROUP: 3-F SEX: FEMALE
DOSE: 1 (mg base/kg/day)

| ANIMAL # | DAY 7[b] | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 | DAY 16 | DAY 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 161 | 0.03 | 0.02 | -0.02 | -0.03 | -0.02 | 0.02 | 0.03 | 0.06 | 0.04 | -0.01 | 0.02 |
| 162 | 0.08 | -0.08 | -0.01 | -0.02 | 0.04 | 0.07 | 0.03 | 0.05 | 0.05 | -0.07 | 0.09 |
| 163 | 0.09 | -0.12 | 0.04 | 0.02 | -0.02 | -0.07 | 0.06 | 0.01 | 0.03 | 0.20 | -0.18 |
| 164 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| 165 | 0.04 | -0.03 | 0.03 | 0.03 | -0.06 | 0.01 | 0.04 | 0.05 | 0.03 | -0.01 | 0.02 |
| MEAN | 0.06 | -0.05 | 0.01 | 0.00 | -0.02 | 0.01 | 0.04 | 0.04 | 0.04 | 0.03 | -0.01 |
| S.D. | 0.029 | 0.061 | 0.029 | 0.029 | 0.041 | 0.058 | 0.014 | 0.022 | 0.010 | 0.118 | 0.116 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

--: Data Unavailable

[a] Successive periods

[b] Baseline is Day 6

DRAFT

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**INDIVIDUAL WEIGHT GAIN** (Kilograms)[a]

STUDY: 137 GROUP: 3-F SEX: FEMALE
DOSE: 1 (mg base/kg/day)

| ANIMAL # | DAY 18 | DAY 29 | TOTAL GAIN |
|---|---|---|---|
| 161 | 0.03 | 0.07 | 0.24 |
| 162 | 0.00 | 0.12 | 0.35 |
| 163 | 0.02 | 0.16 | 0.24 |
| 164 | -- | -- | -- |
| 165 | -0.01 | 0.17 | 0.31 |
| MEAN | 0.01 | 0.13 | 0.29 |
| S.D. | 0.018 | 0.045 | 0.054 |
| N | 4 | 4 | 4 |

--: Data Unavailable b: Scheduled Sacrifice

[a] Successive periods

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 137 GROUP: 4-F SEX: FEMALE
DOSE: 2.5 (mg base/kg/day)

| ANIMAL # | DAY 7[b] | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 | DAY 16 | DAY 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 166 | 0.02 | -0.07 | 0.04 | 0.01 | 0.00 | 0.04 | 0.02 | -0.02 | 0.18 | -0.06 | -0.04 |
| 167 | 0.01 | 0.00 | 0.02 | 0.01 | -0.01 | 0.04 | 0.00 | -0.01 | 0.01 | -0.01 | 0.01 |
| 168 | -0.21 | 0.11 | 0.09 | 0.06 | 0.09 | 0.03 | 0.00 | 0.10 | -0.02 | 0.08 | -0.03 |
| 169 | d | d | d | d | d | d | d | d | d | d | d |
| 170 | 0.03 | -0.02 | 0.07 | -0.01 | 0.00 | -0.06 | -0.01 | 0.02 | 0.04 | -0.18 | -0.03 |
| MEAN | -0.04 | 0.01 | 0.06 | 0.02 | 0.02 | 0.01 | 0.00 | 0.02 | 0.05 | -0.04 | -0.02 |
| S.D. | 0.115 | 0.076 | 0.031 | 0.030 | 0.047 | 0.049 | 0.013 | 0.054 | 0.088 | 0.108 | 0.022 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

--: Data Unavailable d: Sacrificed Moribund

[a] Successive periods

[b] Baseline is Day 6

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 137 GROUP: 4-F SEX: FEMALE
DOSE: 2.5 (mg base/kg/day)

| ANIMAL # | DAY 18 | DAY 29 | TOTAL GAIN |
|---|---|---|---|
| 166 | -0.03 | 0.10 | 0.19 |
| 167 | 0.02 | -0.17 | -0.08 |
| 168 | 0.01 | -0.04 | 0.27 |
| 169 | d | d | -- |
| 170 | 0.01 | 0.19 | 0.05 |
| MEAN | 0.00 | 0.02 | 0.11 |
| S.D. | 0.022 | 0.158 | 0.155 |
| N | 4 | 4 | 4 |

--: Data Unavailable b: Scheduled Sacrifice d: Sacrificed Moribund

[a] Successive periods

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL WEIGHT GAIN (Kilograms) [b]

STUDY: 137 GROUP: 5-F SEX: FEMALE
DOSE: 6 (mg base/kg/day)

| ANIMAL # | DAY 7 [d] | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 | DAY 16 | DAY 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 171 | 0.02 | -0.03 | -0.07 | -0.15 | c | c | c | c | c | c | c |
| 172 | 0.01 | -0.04 | c | c | c | c | c | c | c | c | c |
| 173 | 0.00 | -0.12 | c | c | c | c | c | c | c | c | c |
| 174 | -0.04 | -0.05 | -0.03 | -0.04 | -0.07 | -0.13 | a | a | a | a | a |
| 175 | 0.02 | 0.01 | 0.03 | -0.10 | -0.09 | c | c | c | c | c | c |
| MEAN | 0.00 | -0.05 | -0.02 | -0.10 | -0.08 | -0.13 | -- | -- | -- | -- | -- |
| S.D. | 0.025 | 0.047 | 0.050 | 0.055 | 0.014 | -- | -- | -- | -- | -- | -- |
| N | 5 | 5 | 3 | 3 | 2 | 1 | 0 | 0 | 0 | 0 | 0 |

--: Data Unavailable a: Accidental Death c: Animal Found Dead

[b] Successive periods

[d] Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**INDIVIDUAL WEIGHT GAIN** (Kilograms)[b]

STUDY: 137 GROUP: 5-F SEX: FEMALE
DOSE: 6 (mg base/kg/day)

| ANIMAL # | DAY 18 | DAY 29 | TOTAL GAIN |
|---|---|---|---|
| 171 | c | c | -- |
| 172 | c | c | -- |
| 173 | c | c | -- |
| 174 | a | a | -- |
| 175 | c | c | -- |
| MEAN | -- | -- | -- |
| S.D. | -- | -- | -- |
| N | 0 | 0 | 0 |

--: Data Unavailable a: Accidental Death c: Animal Found Dead

[b]Successive periods

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DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**INDIVIDUAL WEIGHT GAIN** (Kilograms)[a]

STUDY: 137 GROUP: 6-F SEX: FEMALE
DOSE: 14 (mg base/kg/day)

| ANIMAL # | DAY 7[b] | DAY 8 | DAY 9 | DAY 10 | DAY 11 | DAY 12 | DAY 13 | DAY 14 | DAY 15 | DAY 16 | DAY 17 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 176 | -0.02 | c | c | c | c | c | c | c | c | c | c |
| 177 | -- | c | c | c | c | c | c | c | c | c | c |
| 178 | -- | c | c | c | c | c | c | c | c | c | c |
| 179 | 0.06 | c | c | c | c | c | c | c | c | c | c |
| 180 | 0.00 | c | c | c | c | c | c | c | c | c | c |
| MEAN | 0.01 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| S.D. | 0.042 | -- | -- | -- | -- | -- | -- | -- | -- | -- | -- |
| N | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

--: Data Unavailable c: Animal Found Dead

[a] Successive periods

[b] Baseline is Day 6

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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**INDIVIDUAL WEIGHT GAIN** (Kilograms)[a]

STUDY: 137 GROUP: 6-F SEX: FEMALE
DOSE: 14 (mg base/kg/day)

| ANIMAL # | DAY 18 | DAY 29 | TOTAL GAIN |
|---|---|---|---|
| 176 | c | c | -- |
| 177 | c | c | -- |
| 178 | c | c | -- |
| 179 | c | c | -- |
| 180 | c | c | -- |
| MEAN | -- | -- | -- |
| S.D. | -- | -- | -- |
| N | 0 | 0 | 0 |

--: Data Unavailable c: Animal Found Dead

[a]Successive periods

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 137 GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

| ANIMAL # | DAY 8 | DAY 10 | DAY 12 | DAY 15 | DAY 18 | DAY 24 | DAY 29 |
|---|---|---|---|---|---|---|---|
| 151 | 130 | 130 | 130 | 130 | 130 | 130 | 130 |
| 152 | 130 | 130 | 75 | 96 | 130 | 130 | 103 |
| 153 | 130 | 130 | 130 | 107 | 130 | 130 | 65 |
| 154 | 130 | 130 | 130 | 130 | 130 | 130 | 130 |
| 155 | 130 | 126 | 130 | 130 | 130 | 130 | 130 |
| MEAN | 130 | 129 | 119 | 119 | 130 | 130 | 112 |
| S.D. | 0.0 | 1.8 | 24.6 | 16.1 | 0.0 | 0.0 | 28.6 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

--: Data Unavailable

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 137 GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY 8 | DAY 10 | DAY 12 | DAY 15 | DAY 18 | DAY 24 | DAY 29 |
|---|---|---|---|---|---|---|---|
| 156 | 130 | 69 | 130 | 126 | 130 | 130 | 92 |
| 157 | 122 | 130 | 109 | 7 | 48 | 58 | 62 |
| 158 | 130 | 130 | 130 | 130 | 130 | 96 | 103 |
| 159 | 128 | 130 | 130 | 130 | 130 | 130 | 128 |
| 160 | 130 | 109 | 103 | 68 | 93 | 130 | 128 |
| MEAN | 128 | 114 | 120 | 92 | 106 | 109 | 103 |
| S.D. | 3.5 | 26.5 | 13.3 | 54.4 | 36.3 | 32.0 | 27.6 |
| N | 5 | 5 | 5 | 5 | 5 | 5 | 5 |

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 137 GROUP: 3-F SEX: FEMALE
DOSE: 1 (mg base/kg/day)

| ANIMAL # | DAY 8 | DAY 10 | DAY 12 | DAY 15 | DAY 18 | DAY 24 | DAY 29 |
|---|---|---|---|---|---|---|---|
| 161 | 130 | 16 | 125 | 125 | 130 | 130 | 123 |
| 162 | 130 | 130 | 130 | 130 | 130 | 130 | 110 |
| 163 | 76 | 93 | 50 | 29 | 102 | 130 | 130 |
| 164 | -- | -- | -- | -- | -- | -- | -- |
| 165 | 123 | 130 | 130 | 130 | 130 | 130 | 124 |
| MEAN | 115 | 92 | 109 | 104 | 123 | 130 | 122 |
| S.D. | 26.0 | 53.7 | 39.2 | 49.7 | 14.0 | 0.0 | 8.4 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

--: Data Unavailable

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 137 GROUP: 4-F SEX: FEMALE
DOSE: 2.5 (mg base/kg/day)

| ANIMAL # | DAY 8 | DAY 10 | DAY 12 | DAY 15 | DAY 18 | DAY 24 | DAY 29 |
|---|---|---|---|---|---|---|---|
| 166 | 130 | 130 | 130 | 130 | 130 | 130 | 130 |
| 167 | 122 | 130 | 104 | 34 | 56 | 87 | 37 |
| 168 | 90 | 130 | 130 | 130 | 130 | 130 | 130 |
| 169 | d | d | d | d | d | d | d |
| 170 | 130 | 130 | 98 | 2 | 34 | 130 | 95 |
| MEAN | 118 | 130 | 116 | 74 | 88 | 119 | 98 |
| S.D. | 19.0 | 0.0 | 16.9 | 66.0 | 49.9 | 21.5 | 43.9 |
| N | 4 | 4 | 4 | 4 | 4 | 4 | 4 |

--: Data Unavailable d: Sacrificed Moribund

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

DRAFT

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 137 GROUP: 5-F SEX: FEMALE
DOSE: 6 (mg base/kg/day)

| ANIMAL # | DAY 8 | DAY 10 | DAY 12 | DAY 15 | DAY 18 | DAY 24 | DAY 29 |
|---|---|---|---|---|---|---|---|
| 171 | 73 | 0 | c | c | c | c | c |
| 172 | 124 | c | c | c | c | c | c |
| 173 | 80 | c | c | c | c | c | c |
| 174 | 125 | 23 | D | a | a | a | a |
| 175 | 130 | 42 | -- | c | c | c | c |
| MEAN | 106 | 22 | -- | -- | -- | -- | -- |
| S.D. | 27.5 | 21.0 | -- | -- | -- | -- | -- |
| N | 5 | 3 | 1 | 0 | 0 | 0 | 0 |

--: Data Unavailable a: Accidental Death c: Animal Found Dead

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 137 GROUP: 6-F SEX: FEMALE
DOSE: 14 (mg base/kg/day)

| ANIMAL # | DAY 8 | DAY 10 | DAY 12 | DAY 15 | DAY 18 | DAY 24 | DAY 29 |
|---|---|---|---|---|---|---|---|
| 176 | 0 | c | c | c | c | c | c |
| 177 | -- | c | c | c | c | c | c |
| 178 | -- | c | c | c | c | c | c |
| 179 | -- | c | c | c | c | c | c |
| 180 | -- | c | c | c | c | c | c |
| MEAN | -- | -- | -- | -- | -- | -- | -- |
| S.D. | -- | -- | -- | -- | -- | -- | -- |
| N | 1 | 0 | 0 | 0 | 0 | 0 | 0 |

--: Data Unavailable c: Animal Found Dead

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 137
SEX: FEMALE
GROUP: 1-F - 0 mg base/kg/day
FATES: Scheduled Sacrifice DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 151 | 152 | 153 | 154 | 155 |
|---|---|---|---|---|---|
| BODY WEIGHT (KG) | 3.76 | 3.70 | 3.76 | 4.41 | 4.08 |
| Gravid Uterus (G) | 372.13 | 368.48 | 531.80 | 454.73 | 310.47 |
| % BODY WEIGHT | 9.897 | 9.959 | 14.144 | 10.311 | 7.610 |

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 137
SEX: FEMALE
GROUP: 2-F - 0.5 mg base/kg/day
FATES: Scheduled Sacrifice DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 156 | 157 | 158 | 159 | 160 |
|---|---|---|---|---|---|
| BODY WEIGHT (KG) | 4.23 | 3.60 | 3.98 | 3.82 | 4.47 |
| Gravid Uterus (G) | 538.52 | 376.01 | 546.68 | 396.05 | 718.38 |
| % BODY WEIGHT | 12.731 | 10.445 | 13.736 | 10.368 | 16.071 |

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 137
SEX: FEMALE
GROUP: 3-F - 1 mg base/kg/day
FATES: Scheduled Sacrifice DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 161 | 162 | 163 | 165 |
|---|---|---|---|---|
| BODY WEIGHT (KG) | 3.72 | 4.40 | 4.04 | 4.39 |
| Gravid Uterus (G) | 269.45 | 530.94 | 418.57 | 492.32 |
| % BODY WEIGHT | 7.243 | 12.067 | 10.361 | 11.215 |

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL ORGAN WEIGHTS

STUDY: 137
SEX: FEMALE
GROUP: 4-F - 2.5 mg base/kg/day
FATES: Scheduled Sacrifice DAYS: BEGINNING-29 ALL BALANCES

| ANIMAL ID: / BALANCE NO.: | 166 | 167 | 168 | 170 |
|---|---|---|---|---|
| BODY WEIGHT (KG) | 4.39 | 3.57 | 4.24 | 3.75 |
| Gravid Uterus (G) | 416.24 | 393.53 | 307.46 | 462.23 |
| % BODY WEIGHT | 9.482 | 11.023 | 7.251 | 12.326 |

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS

**Individual Maternal Cesarean Section Data**

| Dose Level (mg base/kg/day) | Dam No. | Total Implantations | *Corpora Lutea* | Resorptions | | Viable Fetuses per Dam | Non-Viable Fetuses per Dam | Gross Dam Observations |
|---|---|---|---|---|---|---|---|---|
| | | | | Early | Late | | | |
| 0 | 151 | 8 | 9 | 2 | 0 | 6 | 0 | Normal |
| | 152 | 8 | 8 | 1 | 0 | 7 | 0 | Normal |
| | 153 | 8 | 9 | 0 | 0 | 8 | 0 | Normal |
| | 154 | 8 | 8 | 0 | 0 | 8 | 0 | Normal |
| | 155 | 5 | 6 | 0 | 0 | 5 | 0 | Normal |
| 0.5 | 156 | 10 | 11 | 0 | 0 | 10 | 0 | Normal |
| | 157 | 9 | 10 | 1 | 0 | 8 | 0 | Normal |
| | 158 | 8 | 10 | 0 | 0 | 8 | 0 | Normal |
| | 159 | 6 | 10 | 0 | 0 | 6 | 0 | Normal |
| | 160 | 12 | 17 | 0 | 0 | 12 | 0 | Normal |
| 1 | 161 | 4 | 10 | 0 | 0 | 4 | 0 | Normal |
| | 162 | 10 | 10 | 0 | 1 | 9 | 0 | Normal |
| | 163 | 10 | 10 | 1 | 0 | 9 | 0 | Normal |
| | 165 | 8 | 8 | 0 | 0 | 8 | 0 | Normal |

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS

**Individual Maternal Cesarean Section Data**

| Dose Level (mg base/kg/day) | Dam No. | Pre-Implantation Loss % | Post-Implantation Loss % | Total Loss/Litter % |
|---|---|---|---|---|
| 0 | 151 | 11 | 25 | 33 |
| | 152 | 0 | 13 | 13 |
| | 153 | 11 | 0 | 11 |
| | 154 | 0 | 0 | 0 |
| | 155 | 17 | 0 | 17 |
| 0.5 | 156 | 9 | 0 | 9 |
| | 157 | 10 | 11 | 20 |
| | 158 | 20 | 0 | 20 |
| | 159 | 40 | 0 | 40 |
| | 160 | 29 | 0 | 29 |
| 1 | 161 | 60 | 0 | 60 |
| | 162 | 0 | 10 | 10 |
| | 163 | 0 | 10 | 10 |
| | 165 | 0 | 0 | 0 |

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS

**Individual Maternal Cesarean Section Data**

| Dose Level (mg base/kg/day) | Dam No. | Total Implantations | *Corpora Lutea* | Resorptions | | Viable Fetuses per Dam | Non-Viable Fetuses per Dam | Gross Dam Observations |
|---|---|---|---|---|---|---|---|---|
| | | | | Early | Late | | | |
| 2.5 | 166 | 8 | 10 | 0 | 0 | 8 | 0 | Normal |
| | 167 | 9 | 9 | 1 | 0 | 7 | 1 | Normal |
| | 168 | 5 | 8 | 0 | 0 | 5 | 0 | Normal |
| | 170 | 9 | 8 | 0 | 0 | 9 | 0 | Normal |
| 6 | 171 | 10 | 10 | 10 | 0 | NA | NA | Dead |
| | 172 | 7 | 10 | 0 | 0 | NA | NA | Dead |
| | 173 | 12 | 12 | 0 | 0 | NA | NA | Dead |
| | 174 | 8 | 9 | 0 | 8 | NA | NA | Dead |
| | 175 | 7 | 10 | 0 | 7 | NA | NA | Dead |
| 14 | 176 | 2 | 9 | 2 | 0 | NA | NA | Dead |
| | 179 | 16 | 13 | 3 | 0 | NA | NA | Dead |
| | 180 | 13 | 9 | 6 | 0 | NA | NA | Dead |

NA = Not Applicable

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS

**Individual Maternal Cesarean Section Data**

| Dose Level (mg base/kg/day) | Dam No. | Pre-Implantation Loss % | Post-Implantation Loss % | Total Loss/Litter % |
|---|---|---|---|---|
| 2.5 | 166 | 20 | 0 | 20 |
| | 167 | 0 | 22 | 22 |
| | 168 | 38 | 0 | 38 |
| | 170 | -13 | 0 | -13 |
| 6 | 171 | 0 | NA | 100 |
| | 172 | 30 | NA | 100 |
| | 173 | 0 | NA | 100 |
| | 174 | 11 | NA | 100 |
| | 175 | 30 | NA | 100 |
| 14 | 176 | 78 | NA | 100 |
| | 179 | -23 | NA | 100 |
| | 180 | -44 | NA | 100 |

NA = Not Applicable

# APPENDIX 2

## INDIVIDUAL FETAL DATA

- Fetal Observations
- Individual Body Weights

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7Q
Study No.: 137

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY STUDY OF WR242511 IN RATS

## List of Abbreviations

| | | | | |
|---|---|---|---|---|
| NA = Not applicable<br>N = No visible abnormalities<br>A = Alive<br>D = Dead | R = Right<br>L = Left<br>M = Male<br>F = Female<br>H = Head<br>B= Back | NK = Neck<br>HL = Hind limb<br>FL = Fore limb<br>DI = Digit<br>SC = Scalp<br>TR = Trunk | PT = Protruded tongue<br>SB = Spina bifida<br>SUBQ = Subcutaneous<br>P = Petechial<br>ABD = Abdominal | CP = Cleft palate<br>CL = Cleft lip<br>HT = Hematoma<br>EX = Exophthalmos<br>AN = Anophthalmos<br>EC = Exencephaly<br>MI = Microcephaly |

Note: Fetal animal numbers in the body weight table are expressed as the dam animal number followed by the implantation site. For example: Fetus number 1234 = dam number 123, implantation site no.4

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS
DOSE (0 mg base/kg/day)



| | Date Sac | Implantation Site | Sex | Status | Fetal Body Wt. (g) | External Examination |
|---|---|---|---|---|---|---|
| 151 | 7/25/94 | 1 | M | A | 43.06 | N |
| | | 2 | F | A | 39.56 | N |
| | | 3 | F | A | 35.44 | N |
| | | 4 | M | A | 44.92 | N |
| | | 5 | - | ER | - | Early resorption |
| | | 6 | M | A | 51.19 | N |
| | | 7 | - | ER | - | Early resorption |
| | | 8 | M | A | 49.65 | N |
| 152 | 7/25/94 | 1 | M | A | 39.52 | N |
| | | 2 | M | A | 39.73 | N |
| | | 3 | M | A | 40.51 | N |
| | | 4 | M | A | 32.65 | N |
| | | 5 | F | A | 34.31 | N |
| | | 6 | M | A | 40.42 | N |
| | | 7 | F | A | 42.63 | N |
| | | 8 | - | ER | - | Early resorption |
| 153 | 7/25/94 | 1 | F | A | 47.71 | N |
| | | 2 | M | A | 43.55 | N |
| | | 3 | M | A | 45.43 | N |
| | | 4 | F | A | 45.85 | N |
| | | 5 | F | A | 50.28 | N |
| | | 6 | M | A | 46.19 | N |
| | | 7 | M | A | 51.81 | N |
| | | 8 | M | A | 47.89 | N |
| 154 | 7/26/94 | 1 | F | A | 46.39 | N |
| | | 2 | F | A | 40.50 | N |
| | | 3 | M | A | 40.04 | N |
| | | 4 | F | A | 42.47 | N |
| | | 5 | M | A | 39.13 | N |
| | | 6 | M | A | 39.78 | N |
| | | 7 | F | A | 44.79 | N |
| | | 8 | | A | 46.81 | N |
| 155 | 7/26/94 | 1 | F | A | 44.80 | N |
| | | 2 | M | A | 45.43 | N |
| | | 3 | F | A | 45.44 | N |
| | | 4 | M | A | 48.81 | N |
| | | 5 | F | A | 47.66 | N |

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS
DOSE (0.5 mg base/kg/day)



| | Date Sac | Implantation Site | Sex | Status | Fetal Body Wt. (g) | External Examination |
|---|---|---|---|---|---|---|
| 156 | 7/25/94 | 1 | F | A | 44.40 | N |
| | | 2 | M | A | 35.72 | N |
| | | 3 | M | A | 29.72 | N |
| | | 4 | F | A | 47.51 | N |
| | | 5 | M | A | 38.08 | N |
| | | 6 | F | A | 29.42 | N |
| | | 7 | F | A | 43.16 | N |
| | | 8 | M | A | 46.65 | N |
| | | 9 | F | A | 41.59 | N |
| | | 10 | M | A | 41.87 | N |
| 157 | 7/25/94 | 1 | - | ER | - | Early resorption |
| | | 2 | F | A | 36.30 | N |
| | | 3 | F | A | 33.21 | N |
| | | 4 | F | A | 33.62 | N |
| | | 5 | M | A | 28.88 | N |
| | | 6 | M | A | 30.42 | N |
| | | 7 | F | A | 34.57 | N |
| | | 8 | F | A | 37.88 | N |
| | | 9 | F | A | 40.90 | N |
| 158 | 7/26/94 | 1 | F | A | 49.95 | N |
| | | 2 | F | A | 47.28 | N |
| | | 3 | F | A | 49.90 | N |
| | | 4 | F | A | 53.62 | N |
| | | 5 | F | A | 42.36 | N |
| | | 6 | F | A | 47.03 | N |
| | | 7 | F | A | 49.32 | N |
| | | 8 | M | A | 52.73 | N |
| 159 | 7/26/94 | 1 | M | A | 41.45 | N |
| | | 2 | F | A | 41.79 | N |
| | | 3 | M | A | 44.24 | N |
| | | 4 | F | A | 40.52 | N |
| | | 5 | M | A | 52.02 | N |
| | | 6 | F | A | 43.69 | N |
| 160 | 7/26/94 | 1 | F | A | 44.91 | N |
| | | 2 | F | A | 42.46 | N |
| | | 3 | F | A | 43.66 | N |
| | | 4 | M | A | 41.05 | N |
| | | 5 | M | A | 42.74 | N |
| | | 6 | M | A | 44.15 | N |
| | | 7 | M | A | 46.93 | N |
| | | 8 | M | A | 37.69 | N |
| | | 9 | M | A | 40.54 | N |
| | | 10 | F | A | 43.47 | N |
| | | 11 | F | A | 42.51 | N |
| | | 12 | M | A | 48.80 | N |

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS
DOSE (1 mg base/kg/day)



| | Date Sac | Implantation Site | Sex | Status | Fetal Body Wt. (g) | External Examination |
|---|---|---|---|---|---|---|
| 161 | 7/25/94 | 1 | M | A | 53.59 | N |
| | | 2 | F | A | 49.35 | N |
| | | 3 | M | A | 43.74 | N |
| | | 4 | M | A | 47.99 | N |
| 162 | 7/25/94 | 1 | M | A | 50.66 | N |
| | | 2 | - | LR | - | Late resorption |
| | | 3 | F | A | 43.58 | N |
| | | 4 | F | A | 41.40 | N |
| | | 5 | F | A | 32.50 | N |
| | | 6 | M | A | 36.95 | N |
| | | 7 | M | A | 41.39 | N |
| | | 8 | F | A | 41.98 | N |
| | | 9 | F | A | 37.63 | N |
| | | 10 | M | A | 48.24 | N |
| 163 | 7/25/94 | 1 | - | ER | - | Early resorption |
| | | 2 | F | A | 35.23 | N |
| | | 3 | M | A | 36.51 | N |
| | | 4 | M | A | 32.19 | N |
| | | 5 | M | A | 35.37 | N |
| | | 6 | M | A | 38.65 | N |
| | | 7 | F | A | 33.00 | N |
| | | 8 | F | A | 29.64 | N |
| | | 9 | F | A | 35.55 | N |
| | | 10 | M | A | 38.93 | N |
| 164 | | Animal | was | not | pregnant | |
| 165 | 7/26/94 | 1 | M | A | 44.14 | N |
| | | 2 | F | A | 41.77 | N |
| | | 3 | F | A | 30.25 | N |
| | | 4 | M | A | 44.09 | N |
| | | 5 | F | A | 43.68 | N |
| | | 6 | M | A | 40.28 | N |
| | | 7 | M | A | 48.11 | N |
| | | 8 | F | A | 49.60 | N |

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY
(SEGMENT II) STUDY OF WR242511 IN RABBITS
DOSE (2.5 mg base/kg/day)



| | Date Sac | Implantation Site | Sex | Status | Fetal Body Wt. (g) | External Examination |
|---|---|---|---|---|---|---|
| 166 | 7/25/94 | 1 | M | A | 39.96 | N |
| | | 2 | M | A | 37.17 | N |
| | | 3 | M | A | 39.32 | N |
| | | 4 | F | A | 33.07 | N |
| | | 5 | M | A | 39.56 | N |
| | | 6 | F | A | 34.87 | N |
| | | 7 | F | A | 36.55 | N |
| | | 8 | M | A | 36.26 | N |
| 167 | 7/25/94 | 1 | - | D | 11.69 | Dead |
| | | 2 | M | A | 36.73 | N |
| | | 3 | F | A | 43.15 | N |
| | | 4 | F | A | 44.46 | SUBQ HT R HL foot |
| | | 5 | F | A | 28.57 | N |
| | | 6 | M | A | 29.13 | N |
| | | 7 | - | ER | - | Early resorption |
| | | 8 | F | A | 26.46 | N |
| | | 9 | M | A | 34.90 | N |
| 168 | 7/26/94 | 1 | M | A | 45.25 | N |
| | | 2 | M | A | 42.77 | N |
| | | 3 | F | A | 38.70 | N |
| | | 4 | M | A | 35.34 | N |
| | | 5 | F | A | 37.19 | N |
| 169 | | Animal | was | not | pregnant | |
| 170 | 7/26/94 | 1 | M | A | 40.71 | N |
| | | 2 | M | A | 40.18 | N |
| | | 3 | F | A | 35.88 | N |
| | | 4 | F | A | 36.17 | N |
| | | 5 | F | A | 35.88 | N |
| | | 6 | F | A | 34.68 | N |
| | | 7 | M | A | 39.27 | N |
| | | 8 | M | A | 42.26 | N |
| | | 9 | F | A | 40.33 | N |

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 137L GROUP: 1-M SEX: MALE
DOSE: 0 (mg base/kg/day)

| ANIMAL # | DAY 0 |
|---|---|
| 1511 | 43.06 |
| 1514 | 44.92 |
| 1516 | 51.19 |
| 1518 | 49.65 |
| 1521 | 39.52 |
| 1522 | 39.73 |
| 1523 | 40.51 |
| 1524 | 32.65 |
| 1526 | 40.42 |
| 1532 | 43.55 |
| 1533 | 45.43 |
| 1536 | 46.19 |
| 1537 | 51.81 |
| 1538 | 47.89 |
| 1543 | 40.04 |
| 1545 | 39.13 |
| 1546 | 39.78 |
| 1552 | 45.43 |
| 1554 | 48.81 |
| MEAN | 43.67 |
| S.D. | 4.949 |
| N | 19 |

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL
TOXICITY (SEGMENT II) STUDY OF
WR242511 IN RABBITS

**INDIVIDUAL BODY WEIGHTS** (Grams)

STUDY: 137L GROUP: 1-F SEX: FEMALE
DOSE: 0 (mg base/kg/day)

| ANIMAL # | DAY 0 |
|---|---|
| 1512 | 39.56 |
| 1513 | 35.44 |
| 1525 | 34.31 |
| 1527 | 42.63 |
| 1531 | 47.71 |
| 1534 | 45.85 |
| 1535 | 50.28 |
| 1541 | 46.39 |
| 1542 | 40.50 |
| 1544 | 42.47 |
| 1547 | 44.79 |
| 1551 | 44.80 |
| 1553 | 45.44 |
| 1555 | 47.66 |
| 1548 | 46.81 |
| MEAN | 43.64 |
| S.D. | 4.539 |
| N | 15 |

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**INDIVIDUAL BODY WEIGHTS** (Grams)

STUDY: 137L GROUP: 2-M SEX: MALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY 0 |
|---|---|
| 1562 | 35.72 |
| 1563 | 29.72 |
| 1565 | 38.08 |
| 1568 | 46.65 |
| 15610 | 41.87 |
| 1575 | 28.88 |
| 1576 | 30.42 |
| 1588 | 52.73 |
| 1591 | 41.45 |
| 1595 | 52.02 |
| 1604 | 41.05 |
| 1605 | 42.74 |
| 1606 | 44.15 |
| 1607 | 46.93 |
| 1608 | 37.69 |
| 1609 | 40.54 |
| 16012 | 48.80 |
| 1593 | 44.24 |
| MEAN | 41.32 |
| S.D. | 7.043 |
| N | 18 |

--: Data Unavailable

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 137L GROUP: 2-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY 0 |
|---|---|
| 1561 | 44.40 |
| 1564 | 47.51 |
| 1566 | 29.42 |
| 1567 | 43.16 |
| 1569 | 41.59 |
| 1572 | 36.30 |
| 1573 | 33.21 |
| 1574 | 33.62 |
| 1577 | 34.57 |
| 1578 | 37.88 |
| 1579 | 40.90 |
| 1581 | 49.95 |
| 1582 | 47.28 |
| 1583 | 49.90 |
| 1584 | 53.62 |
| 1585 | 42.36 |
| 1586 | 47.03 |
| 1587 | 49.32 |
| 1592 | 41.79 |
| 1594 | 40.52 |
| 1596 | 43.69 |
| 1601 | 44.91 |
| 1602 | 42.46 |
| 1603 | 43.66 |
| 16010 | 43.47 |
| 16011 | 42.51 |
| MEAN | 42.50 |
| S.D. | 5.759 |
| N | 26 |

--: Data Unavailable

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 137L GROUP: 3-M SEX: MALE
DOSE: 1(mg base/kg/day)

| ANIMAL # | DAY 0 |
|---|---|
| 1611 | 53.59 |
| 1613 | 43.74 |
| 1614 | 47.99 |
| 1621 | 50.66 |
| 1626 | 36.95 |
| 1627 | 41.39 |
| 16210 | 48.24 |
| 1633 | 36.51 |
| 1634 | 32.19 |
| 1635 | 35.37 |
| 1636 | 38.65 |
| 16310 | 38.93 |
| 1651 | 44.14 |
| 1654 | 44.09 |
| 1656 | 40.28 |
| 1657 | 48.11 |
| MEAN | 42.55 |
| S.D. | 6.046 |
| N | 16 |

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

**INDIVIDUAL BODY WEIGHTS** (Grams)

STUDY: 137L GROUP: 3-F SEX: FEMALE
DOSE: 1 (mg base/kg/day)

| ANIMAL # | DAY 0 |
|---|---|
| 1612 | 49.35 |
| 1623 | 43.58 |
| 1624 | 41.40 |
| 1625 | 32.50 |
| 1628 | 41.98 |
| 1629 | 37.63 |
| 1632 | 35.23 |
| 1637 | 33.00 |
| 1638 | 29.64 |
| 1639 | 35.55 |
| 1652 | 41.77 |
| 1653 | 30.25 |
| 1655 | 43.68 |
| 1658 | 49.60 |
| MEAN | 38.94 |
| S.D. | 6.534 |
| N | 14 |

--: Data Unavailable

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## INDIVIDUAL BODY WEIGHTS (Grams)

STUDY: 137L

GROUP: 4-M SEX: MALE

DOSE: 2.5 (mg base/kg/day)

| ANIMAL # | DAY 0 |
|---|---|
| 1661 | 39.96 |
| 1662 | 37.17 |
| 1663 | 39.32 |
| 1665 | 39.56 |
| 1668 | 36.26 |
| 1672 | 36.73 |
| 1676 | 29.13 |
| 1679 | 34.90 |
| 1681 | 45.25 |
| 1682 | 42.77 |
| 1684 | 35.34 |
| 1701 | 40.71 |
| 1702 | 40.18 |
| 1707 | 39.27 |
| 1708 | 42.26 |
| MEAN | 38.59 |
| S.D. | 3.880 |
| N | 15 |

--: Data Unavailable

DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

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**INDIVIDUAL BODY WEIGHTS** (Grams)

STUDY: 137L GROUP: 4-F SEX: FEMALE
DOSE: 2.5 (mg base/kg/day)

| ANIMAL # | DAY 0 |
|---|---|
| 1664 | 33.07 |
| 1666 | 34.87 |
| 1667 | 36.55 |
| 1673 | 43.15 |
| 1674 | 44.46 |
| 1675 | 28.57 |
| 1678 | 26.46 |
| 1683 | 38.70 |
| 1685 | 37.19 |
| 1703 | 35.88 |
| 1704 | 36.17 |
| 1705 | 35.88 |
| 1706 | 34.68 |
| 1709 | 40.33 |
| MEAN | 36.14 |
| S.D. | 4.868 |
| N | 14 |

--: Data Unavailable

# APPENDIX 3

## PRELIMINARY RANGE-FINDING TEST DATA

- Summary of Clinical Signs
- Summary of Body Weights
- Summary of Weight Gains
- Summary of Daily Mean Food Consumption
- Individual Observations
- Individual Body Weights
- Individual Weight Gain
- Individual Daily Food Consumption

## SUMMARY OF CLINICAL SIGNS

STUDY: 137R SEX: FEMALE

| DOSE: (mg base/kg/day) | 0.5 | 2[a] | 6 |
|---|---|---|---|
| GROUP: | 1-F | 2-F | 3-F |
| Animal Found Dead | 0 | 1 | 0 |
| Decreased Activity | 0 | 2 | 0 |
| Total Number of Animals | 2 | 2 | 2 |

[a] dose was escalated twice, to 12 mg base/kg/day after 6 days and to 24 mg base/kg/day after 8 days

## SUMMARY OF BODY WEIGHTS (Kilograms)

STUDY: 137R SEX: FEMALE

| PERIOD | DOSE: GROUP: | 0.5 1-F | 2[a] 2-F | 6 3-F | (mg base/kg/day) |
|---|---|---|---|---|---|
| DAY -2 | MEAN | 2.44 | 2.33 | 2.35 | |
| | S.D. | 0.205 | 0.198 | 0.099 | |
| | N | 2 | 2 | 2 | |
| DAY 0 | MEAN | 2.40 | 2.35 | 2.38 | |
| | S.D. | 0.141 | 0.184 | 0.007 | |
| | N | 2 | 2 | 2 | |
| DAY 4 | MEAN | 2.49 | 2.42 | 2.39 | |
| | S.D. | 0.113 | 0.141 | 0.057 | |
| | N | 2 | 2 | 2 | |
| DAY 7 | MEAN | 2.54 | 2.47 | 2.44 | |
| | S.D. | 0.127 | 0.120 | 0.092 | |
| | N | 2 | 2 | 2 | |
| DAY 10 | MEAN | 2.52 | 2.42 | 2.47 | |
| | S.D. | 0.163 | 0.191 | 0.071 | |
| | N | 2 | 2 | 2 | |
| DAY 13 | MEAN | 2.56 | 2.32 | 2.49 | |
| | S.D. | 0.212 | 0.000 | 0.071 | |
| | N | 2 | 1 | 2 | |

[a] dose was escalated twice, to 12 mg base/kg/day after 6 days and to 24 mg base/kg/day after 8 days

# 13 DAY RANGE-FINDING TEST OF WR242511 IN FEMALE RABBITS

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## SUMMARY OF WEIGHT GAINS (Kilograms)

STUDY: 137R SEX: FEMALE

| PERIOD | DOSE: GROUP: | 0.5 1-F | 2[a] 2-F | 6 (mg base/kg/day) 3-F |
|---|---|---|---|---|
| DAY 4 | MEAN | 0.09 | 0.07 | 0.02 |
| | S.D. | 0.028 | 0.042 | 0.064 |
| | N | 2 | 2 | 2 |
| DAY 7 | MEAN | 0.05 | 0.05 | 0.05 |
| | S.D. | 0.014 | 0.021 | 0.035 |
| | N | 2 | 2 | 2 |
| DAY 10 | MEAN | -0.03 | -0.05 | 0.04 |
| | S.D. | 0.035 | 0.071 | 0.021 |
| | N | 2 | 2 | 2 |
| DAY 13 | MEAN | 0.05 | -0.23 | 0.02 |
| | S.D. | 0.049 | 0.000 | 0.000 |
| | N | 2 | 1 | 2 |
| TOTAL GAIN | MEAN | 0.16 | -0.16 | 0.12 |
| | S.D. | 0.071 | 0.000 | 0.078 |
| | N | 2 | 1 | 2 |

[a]dose was escalated twice, to 12 mg base/kg/day after 6 days and to 24 mg base/kg/day after 8 days

## SUMMARY OF DAILY MEAN FOOD CONSUMPTION (Grams)

STUDY: 137R SEX: FEMALE

| PERIOD | DOSE: (mg base/kg/day) / GROUP: | 0.5 1-F | 2 [a] 2-F | 6 3-F |
|---|---|---|---|---|
| DAY -1 | INTAKE (g) | 130 | 130 | 130 |
| | S.D. | 0.0 | 0.0 | 0.0 |
| | N | 2 | 2 | 2 |
| DAY 1 | INTAKE (g) | 130 | 130 | 130 |
| | S.D. | 0.0 | 0.0 | 0.0 |
| | N | 2 | 2 | 2 |
| DAY 5 | INTAKE (g) | 130 | 130 | 130 |
| | S.D. | 0.0 | 0.0 | 0.0 |
| | N | 2 | 2 | 2 |
| DAY 8 | INTAKE (g) | 130 | 130 | 130 |
| | S.D. | 0.0 | 0.0 | 0.0 |
| | N | 2 | 2 | 2 |
| DAY 12 | INTAKE (g) | 130 | 60 | 128 |
| | S.D. | 0.0 | 0.0 | 3.5 |
| | N | 2 | 1 | 2 |

[a] dose was escalated twice, to 12 mg base/kg/day after 6 days and to 24 mg base/kg/day after 8 days

13 DAY RANGE-FINDING TEST OF
WR242511 IN FEMALE RABBITS

**INDIVIDUAL CLINICAL SIGNS**

STUDY: 137R
DAY 0-DAY 13

GROUP: 1-F
DOSE: 0.5 (mg base/kg/day)

SEX: FEMALE

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 126 | Normal | | | DAY 0-DAY 12 |
| 127 | Normal | | | DAY 0-DAY 12 |

## INDIVIDUAL CLINICAL SIGNS

STUDY: 137R
DAY 0-DAY 13

GROUP: 2-F
DOSE: 2/12/24 (mg base/kg/day)[a]

SEX: FEMALE

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 128 | Decreased Activity | | | DAY 11-DAY 12 |
| | Normal | | | DAY 0-DAY 10 |
| 129 | Decreased Activity | | | DAY 10 |
| | Animal Found Dead | | | DAY 11 |
| | Normal | | | DAY 0-DAY 9 |

[a] dose was escalated twice, to 12 mg base/kg/day after 6 days and to 24 mg base/kg/day after 8 days

13 DAY RANGE-FINDING TEST OF
WR242511 IN FEMALE RABBITS

**INDIVIDUAL CLINICAL SIGNS**

STUDY: 137R
DAY 0-DAY 13

GROUP: 3-F
DOSE: 6 (mg base/kg/day)

SEX: FEMALE

| ANIMAL # | OBSERVATIONS | SEVERITY | LOC | TIME OCCURRED |
|---|---|---|---|---|
| 130 | Normal | | | DAY 0-DAY 12 |
| 131 | Normal | | | DAY 0-DAY 12 |

# 13 DAY RANGE-FINDING TEST OF WR242511 IN FEMALE RABBITS

## INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 137R GROUP: 1-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY -2 | DAY 0 | DAY 4 | DAY 7 | DAY 10 | DAY 13 |
|---|---|---|---|---|---|---|
| 126 | 2.58 | 2.50 | 2.57 | 2.63 | 2.63 | 2.71 |
| 127 | 2.29 | 2.30 | 2.41 | 2.45 | 2.40 | 2.41 |
| MEAN | 2.44 | 2.40 | 2.49 | 2.54 | 2.52 | 2.56 |
| S.D. | 0.205 | 0.141 | 0.113 | 0.127 | 0.163 | 0.212 |
| N | 2 | 2 | 2 | 2 | 2 | 2 |

--: Data Unavailable

## INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 137R GROUP: 2-F SEX: FEMALE
DOSE: 2/12/24 (mg base/kg/day)[a]

| ANIMAL # | DAY -2 | DAY 0 | DAY 4 | DAY 7 | DAY 10 | DAY 13 |
|---|---|---|---|---|---|---|
| 128 | 2.47 | 2.48 | 2.52 | 2.55 | 2.55 | 2.32 |
| 129 | 2.19 | 2.22 | 2.32 | 2.38 | 2.28 | c |
| MEAN | 2.33 | 2.35 | 2.42 | 2.47 | 2.42 | 2.32 |
| S.D. | 0.198 | 0.184 | 0.141 | 0.120 | 0.191 | -- |
| N | 2 | 2 | 2 | 2 | 2 | 1 |

--: Data Unavailable c: Animal Found Dead

[a]dose was escalated twice, to 12 mg base/kg/day after 6 days and to 24 mg base/kg/day after 8 days

# 13 DAY RANGE-FINDING TEST OF WR242511 IN FEMALE RABBITS

## INDIVIDUAL BODY WEIGHTS (Kilograms)

STUDY: 137R GROUP: 3-F SEX: FEMALE
DOSE: 6 (mg base/kg/day)

| ANIMAL # | DAY -2 | DAY 0 | DAY 4 | DAY 7 | DAY 10 | DAY 13 |
|---|---|---|---|---|---|---|
| 130 | 2.28 | 2.38 | 2.35 | 2.37 | 2.42 | 2.44 |
| 131 | 2.42 | 2.37 | 2.43 | 2.50 | 2.52 | 2.54 |
| MEAN | 2.35 | 2.38 | 2.39 | 2.44 | 2.47 | 2.49 |
| S.D. | 0.099 | 0.007 | 0.057 | 0.092 | 0.071 | 0.071 |
| N | 2 | 2 | 2 | 2 | 2 | 2 |

--: Data Unavailable

# 13 DAY RANGE-FINDING TEST OF WR242511 IN FEMALE RABBITS

## INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 137R GROUP: 1-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY 4[b] | DAY 7 | DAY 10 | DAY 13 | TOTAL GAIN |
|---|---|---|---|---|---|
| 126 | 0.07 | 0.06 | 0.00 | 0.08 | 0.21 |
| 127 | 0.11 | 0.04 | -0.05 | 0.01 | 0.11 |
| MEAN | 0.09 | 0.05 | -0.03 | 0.05 | 0.16 |
| S.D. | 0.028 | 0.014 | 0.035 | 0.049 | 0.071 |
| N | 2 | 2 | 2 | 2 | 2 |

--: Data Unavailable

[a] Successive periods

[b] Baseline is Day -2

# 13 DAY RANGE-FINDING TEST OF WR242511 IN FEMALE RABBITS

## INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 137R GROUP: 2-F SEX: FEMALE
DOSE: 2/12/24 (mg base/kg/day)[b]

| ANIMAL # | DAY 4[d] | DAY 7 | DAY 10 | DAY 13 | TOTAL GAIN |
|---|---|---|---|---|---|
| 128 | 0.04 | 0.03 | 0.00 | -0.23 | -0.16 |
| 129 | 0.10 | 0.06 | -0.10 | c | -- |
| MEAN | 0.07 | 0.05 | -0.05 | -0.23 | -0.16 |
| S.D. | 0.042 | 0.021 | 0.071 | -- | -- |
| N | 2 | 2 | 2 | 1 | 1 |

--: Data Unavailable c: Animal Found Dead

[a] Successive periods

[b] Dose was escalated twice, to 12 mg base/kg/day after 6 days and to 24 mg base/kg/day after 8 days

[d] Baseline is Day -2

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## INDIVIDUAL WEIGHT GAIN (Kilograms)[a]

STUDY: 137R GROUP: 3-F SEX: FEMALE
DOSE: 6 (mg base/kg/day)

| ANIMAL # | DAY 4[b] | DAY 7 | DAY 10 | DAY 13 | TOTAL GAIN |
|---|---|---|---|---|---|
| 130 | -0.03 | 0.02 | 0.05 | 0.02 | 0.06 |
| 131 | 0.06 | 0.07 | 0.02 | 0.02 | 0.17 |
| MEAN | 0.02 | 0.05 | 0.04 | 0.02 | 0.12 |
| S.D. | 0.064 | 0.035 | 0.021 | 0.000 | 0.078 |
| N | 2 | 2 | 2 | 2 | 2 |

--: Data Unavailable

[a] Successive periods

[b] Baseline is Day -2

# 13 DAY RANGE-FINDING TEST OF WR242511 IN FEMALE RABBITS

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 137R GROUP: 1-F SEX: FEMALE
DOSE: 0.5 (mg base/kg/day)

| ANIMAL # | DAY -1 | DAY 1 | DAY 5 | DAY 8 | DAY 12 |
|---|---|---|---|---|---|
| 126 | 130 | 130 | 130 | 130 | 130 |
| 127 | 130 | 130 | 130 | 130 | 130 |
| MEAN | 130 | 130 | 130 | 130 | 130 |
| S.D. | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| N | 2 | 2 | 2 | 2 | 2 |

--: Data Unavailable

# 13 DAY RANGE-FINDING TEST OF WR242511 IN FEMALE RABBITS

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 137R GROUP: 2-F SEX: FEMALE
DOSE: 2/12/24 (mg base/kg/day)[a]

| ANIMAL # | DAY -1[c] | DAY 1 | DAY 5 | DAY 8 | DAY 12 |
|---|---|---|---|---|---|
| 128 | 130 | 130 | 130 | 130 | 60 |
| 129 | 130 | 130 | 130 | 130 | c |
| MEAN | 130 | 130 | 130 | 130 | 60 |
| S.D. | 0.0 | 0.0 | 0.0 | 0.0 | -- |
| N | 2 | 2 | 2 | 2 | 1 |

--: Data Unavailable c: Animal Found Dead

[a]dose was escalated twice, to 12 mg base/kg/day after 6 days and to 24 mg base/kg/day after 8 days

## INDIVIDUAL DAILY FOOD CONSUMPTION (Grams)

STUDY: 137R GROUP: 3-F SEX: FEMALE
DOSE: 6 (mg base/kg/day)

| ANIMAL # | DAY -1 | DAY 1 | DAY 5 | DAY 8 | DAY 12 |
|---|---|---|---|---|---|
| 130 | 130 | 130 | 130 | 130 | 130 |
| 131 | 130 | 130 | 130 | 130 | 125 |
| MEAN | 130 | 130 | 130 | 130 | 128 |
| S.D. | 0.0 | 0.0 | 0.0 | 0.0 | 3.5 |
| N | 2 | 2 | 2 | 2 | 2 |

--: Data Unavailable

# APPENDIX 4

Protocol and Amendments

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Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7M
Study No.: 137

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## 1.0 PURPOSE OF THE STUDY:

The purpose of this study is to provide information for use in selection of dose levels of the test article for a developmental toxicity study in rabbits. The protocol for this study was approved by the UIC Animal Care Committee (Appendix 1).

## 2.0 SPONSOR:

| | | |
|---|---|---|
| 2.1 | Name: | U.S. Army Medical Materiel Development Activity |
| 2.2 | Address: | Fort Detrick<br>Frederick, MD 21702-5009 |
| 2.3 | Representative: | George J. Schieferstein, Ph.D. |

## 3.0 TESTING FACILITY:

| | | |
|---|---|---|
| 3.1 | Name: | Toxicology Research Laboratory (TRL) |
| 3.2 | Address: | University of Illinois at Chicago (UIC)<br>Department of Pharmacology<br>1940 W. Taylor St.<br>Chicago, IL 60612-7353 |
| 3.3 | Study Director: | Barry S. Levine, D.Sc., D.A.B.T. |

## 4.0 DATES:

| | | |
|---|---|---|
| 4.1 | Proposed Initiation of In-Life Phase: | 7/02/94 |
| 4.2 | Proposed Completion of In-Life Phase: | 7/26/94 |
| 4.3 | Proposed Study Completion Date (Draft Final Report): | 9/26/94 |

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## 5.0 TEST ARTICLE

5.1 Name or Code No: WR242511 Tartrate
Bottle Number - BM05816

5.2 TRL Chemical No: 1720614

5.3 Physical Description: Yellow powder

5.4 Storage Conditions to Maintain Stability:

5.4.1 Temperature: -20 to -15°C.

5.4.2 Humidity: Ambient conditions at -20 to -15°C.

5.4.3 Light: Protect from light.

5.4.4 Special Requirements: None.

5.5 Special Handling Procedures: Standard safety precautions will be followed including gloves, eye protection, mask, and lab coats.

5.6 Log of Test Article: The amount, date, identity of person(s) removing aliquots and the purpose for which each aliquot of the test article was removed from the batch will be documented. At termination of the study, all unused test article will be returned to the Sponsor.

## 6.0 PERSONNEL:

| | |
|---|---|
| Study Director | Barry S. Levine, D.Sc., D.A.B.T. |
| Reproductive Toxicologist | Ashraf F. Youssef, M.D., Ph.D. |
| Reproductive Scientist | Robert A. Matamoros, D.V.M., Ph.D. |
| Analytical Chemist | Adam Negrusz, Ph.D. |
| Clinical Veterinarian | James Artwohl, D.V.M., M.S., D.A.C.L.A.M. |
| Veterinarian Support | Documented in raw data |
| Tox. Lab Supervisor | Soudabeh Soura, B.S. |
| Lead Technician | Documented in raw data |
| Chemistry Specialist | Thomas Tolhurst, B.S. |



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7.0 TEST SYSTEM:

| | | |
|---|---|---|
| 7.1 | Species: | Rabbit |
| 7.2 | Strain: | New Zealand White (Pasteurella Free) |
| 7.3 | No and Sex(s): | 30 time-mated females |
| 7.4 | Weight of Animals: | 3.0 - 4.0 kg at start of study |
| 7.5 | Age of Animals: | 5 to 6 months at study initiation. The animal supplier will provide birth dates on individual animals. |
| 7.6 | Source of Animals: | HRP, Inc.<br>Denver, PA |

7.7 Justification for Selection of Test System: The FDA requires the use of two animal species, one being a non-rodent, in preclinical developmental toxicity studies. The rabbit is a standard and accepted non-rodent species for regulatory developmental toxicology studies, and is specified by the Sponsor. In addition, the New Zealand white rabbit was selected because it has demonstrated sensitivity to developmental toxicants and historical data and experience exist.

7.8 Procedure for Unique Identification of Test System: Each animal will be given a facility-unique number (ear-tag) by the Supplier, and a study-unique number (ear-tag) upon arrival at UIC. This latter number will also appear on a cage card visible on the front of each cage. The cage card will additionally contain the study number, test or control article identification, dose level, and treatment group. Raw data records and specimens will also be identified by the unique animal number.

7.9 Housing: The animals will be housed in an AAALAC-accredited facility. Animals will be singly housed in stainless steel cages in a temperature (61-69°F) and humidity (30 - 70%) controlled room with a 14 hour light/10 hour dark cycle. The cage size, 0.32 $m^2$ area and 38.0 cm height, is adequate to house rabbits for this study as described in the *Guide for the Care and Use of Laboratory Animals*, DHHS (NIH) No. 86.23.

7.10 Quarantine Procedure: Animals will be quarantined for at least 3 days during time from receipt until dosing is initiated on day 6 of gestation. During the quarantine period, the animals will be observed daily for signs of illness and all unusual observations will be reported to the Study Director, Toxicologist or Veterinarian. Animals will be examined during quarantine and approved for use by the veterinarian prior to being placed on test. Any sickly animal will be either eliminated prior to the test animal selection process or replaced by a healthy animal following this procedure but prior to initiation of treatment under the direction of the Study Director or Toxicologist. Quarantine release will be documented on the Clinical Veterinarian Log by a veterinarian prior to study initiation.



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STUDY NO: 137 INITIAL:
DATE: 3/6/96

7.11 Food: The animals will be fasted on the day of arrival. They will receive approximately 25 g of Purina High Fiber Certified Rabbit Chow #5325 (Ralston Purina Company, St. Louis, MO) on the second day, which will be gradually increased over a few days to approximately 100-130 g/day. This regimen is recommended by the animal supplier (HRP, Inc.) to reduce the incidence of intestinal problems. On the days of measured food consumption, an exact amount of 130 g will be provided.

7.12 Water: Tap water from an automatic watering system in which the room distribution lines are flushed daily will be provided *ad libitum* from arrival until termination. The water is untreated with additional chlorine or HCl.

7.13 There are no known contaminants in the feed or water which are expected to influence the study. A copy of the feed certification will be kept with the study records. The results of the most current comprehensive chemical analyses of Chicago water are documented in files maintained by Quality Assurance.

7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures.

## 8.0 EXPERIMENTAL DESIGN:

### 8.1 Treatment Groups:

| Group No. | Dose Level (mg base/kg/day) | Number of Females* |
|---|---|---|
| 1 | 0 | 5 |
| 2 | 0.5 | 5 |
| 3 | 1 | 5 |
| 4 | 2.5 | 5 |
| 5 | 6 | 5 |
| 6 | 14 | 5 |

* Presumed Pregnant

Dose levels of WR242511 will be selected on the basis of a preliminary range-finding test (Section 8.6a). The number of animals, 5/dose level, is the number of animals typically used in preliminary dose range-finding developmental toxicity studies and is the number of animals indicated by the Sponsor in Task Order UIC-7, Modification 3.

8.2 Frequency and Route of Administration of Test Article: The test article will be administered once daily by gavage during the period of major organogenesis. gestation days 6 through 18. It will be given at a dosing volume of 1 ml/kg. Control animals will receive the vehicle at the same dosing volume. The specific volume to be administered will be adjusted on the basis of each animal's most recent body weight.



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DATE: [illegible]

8.3 Justification of Route(s): The oral route is a convenient and accepted procedure for administering a specific amount of a test article to each animal. It mimics potential human exposure conditions and is specified by the Sponsor.

8.4 Procedure to Control Bias during the Assignment of Animals to Treatment Groups: During the quarantine/pretest period, animals judged to be healthy and meeting acceptable body weight requirements will be assigned to the study at random using a randomization procedure on the basis of body weight.

8.5 Test Article Vehicle: 1% Methylcellulose/0.2% Tween 80.

8.6 Test Article Dosage Form Preparation and Analyses: The dosage formulations for the test article will be prepared daily by diluting a stock formulation (made weekly) to appropriate concentration. Stability data obtained from a previous study (UIC/TRL Study No. 106) indicated that the dosing suspensions are stable for 48 hours at the dosage formulations being tested, and the stock formulation is stable for two weeks. Homogeneity data obtained from UIC/TRL Study No. 107 demonstrated that the test article suspensions are homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

The stock test article suspension will be prepared by suspending the appropriate quantity of test article in the vehicle using a mortar and pestle. Stock and dosing suspensions will be stored at 0 - 4°C. Dosing suspensions will not be analyzed as this is a preliminary dose range-finding test and not a GLP compliant study.

8.6a Preliminary Range-Finding Test: Two nonpregnant animals/dose (3 dose levels) will be dosed with the test article for up to 13 days. The doses will be selected based on the dose-range finding study in rats (UIC/TRL Study No. 143). Doses may be adjusted during the treatment period to demonstrate toxicity. Clinical signs will be recorded daily. Body weight and food consumption will be collected at pretest and approximately on days 0, 4, 7, 10, and 13.

8.7 Frequency of Observations, Test Analyses and Measurements:

8.7.1 Mortality Check: All animals will be observed twice daily, at least six hours apart for moribundity/mortality.

8.7.2 Clinical Signs: All animals will be observed daily for clinical signs of toxicity approximately 1-2 hours after dosing, and in the morning after completion of the dosing period. Moribund animals will be sacrificed on that day and the uteine contents will be examined as described in Section 8.7.6.

8.7.3 Body Weights: Individual body weights will be recorded on day 0 of gestation, at randomization, and on gestation days 6-18, 24 and 29.



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8.7.4 Food Consumption: Food consumption for all animals will be measured during the following 24 hour intervals: gestation days 7/8, 9/10, 11/12, 14/15, 17/18, 23/24, and 28/29.

8.7.5 Sacrifice: On day 29 of presumed gestation, all surviving female rabbits will be killed by intravenous injection of sodium pentobarbital (50 mg/kg) via the marginal ear vein.

8.7.6 Cesarean-Sectioning Observations: The abdominal and thoracic cavities will be opened by a ventral midline incision and the contents examined. In gravid animals, the ovaries will be examined. The number of corpora lutea on each ovary will be recorded (ovaries discarded after evaluation). The gravid uterus will be examined and weighed. The number and location of viable and nonviable fetuses* *in utero*, early and late resorptions** and the total number of implantation sites will be recorded.

The uterine position of each fetus will be documented using the following procedure. All implantation sites, including resorptions, will be numbered in consecutive fashion beginning with the left distal uterine horn, noting the position of the cervix, and continuing from the proximal to the distal right uterine horn. Maternal tissues will only be saved for histopathological examination in 10% neutral buffered formalin as deemed necessary by the gross findings. The carcass of each dam will then be discarded.

*A viable fetus is defined as one which responds to stimuli. A nonviable fetus is defined as a term fetus, which does not respond to stimuli *in utero* or is not breathing.

**An early resorption is defined as one in which it is not grossly evident that organogenesis has occurred. A late resorption is defined as one in which it is grossly evident that organogenesis has occurred. A fetus with evident autolysis is considered a late resorption.

8.7.7 Confirmation of Pregnancy: Uteri from females that appear nongravid will be opened and placed for appriximately 10 minutes in ammonium sulfide solution (0.5%) for detection of possible implantation sites. If implantation site is detected, the ovaries will be examined as in 8.7.6.

8.7.8 Necropsy: Animals which die on test or are sacrificed if moribund will be will be examined as soon as possible on the day of death for the cause of death. Examination will not be performed if precluded by postmortem autolysis. Pregnancy status and uterine contents will be recorded. Maternal tissues with gross lesions appropriate for retention will be fixed in neutral buffered 10% formalin for possible future evaluation as deemed necessary. Exception:



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(Paraovarian cysts will be discarded; these are common spontaneous lesions in rabbits). Viscera which appear normal will be discarded. Naturally-delivered pups will be examined to the extent possible using the same methods described for fetuses.

8.7.9 Fetal Observations:

8.7.9.1 Body Weight and Sex: The number of fetuses will be recorded. Each fetus will be individually weighed and sexed.

8.7.9.2 Gross External Examination: All fetuses will be observed externally and the findings recorded. All fetuses will be euthanized by ip injection of a 0.6% solution of pentobarbital (0.3 ml/fetus). Fetuses with gross external alterations will be preserved in Bouin's solution. All other fetuses will be discarded.

8.7.10 Statistical Analyses: Maternal body weights, weight gains, uterine absolute and relative weight (% body weight), and fetal body weight will be analyzed by one-way analysis of variance. If a significant F ratio is obtained ($p \leq 0.05$), Dunnetts test will be used for pair-wise comparisons to the control group. Food consumption data will be analyzed by the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pair-wise comparisons to the control group.

The mean numbers of resorptions, nonviable fetuses, viable fetuses, corpora lutea (C.L.), implantations, preimplantation loss* and postimplantation deaths** will be compared using the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pairwise comparisons to the control group.

*Preimplantation loss = # C.L. - # implantations

**Postimplantation death = # implantations - # live fetuses

The incidence of maternal and fetal observations will be determined, however statistical analyses may not be conducted due to the small number of animals in each group. If indicated, statistical analyses will be performed using nonparametric statistics such as log linear models, the Chi-square test, and/or Fisher's exact probability test.

Quantitative data will be tabulated and presented in the report. In addition to the written report, summary data tables of parameters and variability will be transmitted to the Sponsor on magnetic media (computer diskette) in "ASCII" form. The transcribed data on disk will no longer be considered GLP compliant.



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9.0 RECORDS TO BE MAINTAINED:

All data generated during the conduct of the study, except those that are generated as direct computer input, shall be recorded directly, promptly, and accurately in ink in bound books with prenumbered pages or on worksheets that shall be bound during or at the conclusion of the nonclinical laboratory study. All appropriate computer and machine output shall be bound during or at the conclusion of the study. All data entries shall be dated on the day of entry and signed or initialed by the person entering the data.

Any changes in entries for whatever reason (e.g., to correct an error or transposition) shall be made so as not to obscure the original entry, shall indicate the reason for such change, and shall be dated and signed or identified at the time of data input. In computer driven collection systems, the operator responsible for direct data input shall be identified at the time of data input. Any changes in computer entries for whatever reason (e.g., to correct an error or transposition) shall be made in such a manner so as not to obscure the original entry, if possible, shall indicate the reason for such change, and shall be dated and the responsible individual shall be identified.

All recorded data shall be reviewed, signed, and dated by a knowledgeable person, other than the person making the entry, to assure adherence to procedures and to verify observations.

Upon completion of the study and submission of the final report, all raw data, documentation, specimens, test article reserves and other materials necessary to reconstruct the study will be stored in the TRL archives maintained by Quality Assurance.

All changes or revisions, and reasons therefore, to this protocol once it is approved shall be documented, signed by the Study Director and Sponsor, dated and maintained with the protocol.

10.0 REGULATORY REQUIREMENTS:

This study will be performed within the spirit of the UIC/TRL Quality Assurance Program designed to conform with FDA Good Laboratory Practice Regulations and EPA Good Laboratory Practice Standards.

Will this study be submitted to a regulatory agency? Yes If so, to which agency(ies)? Food and Drug Administration
Does the Sponsor Request that test article samples be returned? Possibly; direction will be provided by the Sponsor.
Does the Sponsor request that samples of the test article/carrier mixture(s) be returned to the Sponsor? No

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Task Order No.: UIC-7M
Study No.: 137

11.0 PROTOCOL APPROVAL:

STUDY DIRECTOR: Barry S. Levine, D.Sc., D.A.B.T. — Date: 11/19/93

SPONSOR APPROVAL: George J. Schieferstein, Ph.D.
Contracting Officer's
Representative (COR) — Date: 12/13/93

COMMENTS FROM THE COR:

UIC The University of Illinois at Chicago

Office of the Vice Chancellor for Research (M/C 672)
310 Administrative Office Building
1737 West Polk Street
Chicago, Illinois 60612-7227
(312) 996-4995

DRAFT

Appendix 1

November 22,1993

Barry S. Levine
Med-Pharmacology
312 BGRC, M/C 868

Dear Dr. Levine:

The protocol indicated below has been reviewed in accordance with the Animal Care Policies of the University of Illinois at Chicago and approved on July 20, 1993.

**Title of Application:** **Dose Range-Finding Developmental Toxicity Study of WR242511 In Rabbits**

**ACC Number: 93-077-7**

This institution has Animal Welfare Assurance Number A3460.01 on file with the Office for Protection from Research Risks, NIH. Please transmit this letter of acceptable verification of your research protocol to your sponsor.

Thank you for complying with the Animal Care Policies and Procedures of UIC.

Sincerely yours,

Josephine B. Miller, Ph.D.
Chair, Animal Care Committee

JBM:st
xc:BRL

DRAFT

# PROTOCOL AMENDMENT

Study No.: 137

Title: Dose Range-Finding Developmental Toxicity Study of WR242511 in Rabbits

1. Page 2 Section 5.1

Indicate the Bottle Number of the test article; "BM05816".

Reason: Sponsor requested that the specific bottle number be included in the protocol.

2. Page 4 Section 7

Add the following section:

"7.14 It is not known if the animals will experience pain or distress during the study. Analgesic or anesthetic agents will confound the ability to determine the toxic potential of the test article, and therefore will not be used. If an animal is in severe pain or distress, following consultation with the veterinary staff, it will be euthanized in accordance with standard operating procedures."

Reason: Sponsor requested addition to the protocol.

3. Page 3 Section 7.3

Delete from the text "unconfirmed".

Reason: Time mated females will be provided.

4. Page 3 Section 7.10

Replace the first sentence to read "Animals will be quarantined for at least 3 days during the time of receipt until dosing is initiated on day 6 of gestation."

Reason: Clarification of the period of quarantine.

5. Page 4 Section 7.11

Add the following sentence: "On the days of measured food consumption an exact amount of 130 g will be provided."

Reason: Clarification of the procedure of measuring food consumption.

6. Page 4 Section 8.1

Add the following sentence to the first paragraph "The number of animals, 5/dose level, is the number of animals typically used in preliminary dose range-finding developmental toxicity studies and is the number of animals indicated by the Sponsor in Task Order UIC-7, Modification 3."

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PROTOCOL AMENDMENT

Study No.: 137

Title: Dose Range-Finding Developmental Toxicity Study of WR242511 in Rabbits

(6 contd.)
Reason: Sponsor requested addition to the protocol.

7. Page 4 Section 8.2

Change dosing volume from "5 ml/kg" to "1 ml/kg".

Reason: Mistake in the protocol.

8. Page 5 Section 8.6

Change the text as follows to indicate that stability and homogeneity testing have been performed in previous toxicity studies; "The dosage formulations for the test article will be prepared daily by diluting a stock formulation (made weekly) to appropriate concentration. Stability data obtained from a previous study (UIC/TRL Study No. 106) indicated that the dosing suspensions are stable for 48 hours at the dosage formulations being tested, and the stock formulation is stable for two weeks. Homogeneity data obtained from UIC/TRL Study No. 107 demonstrated that the test article suspensions are homogeneous (coefficients of variation for sampling in the top, middle and bottom of several test suspensions were typically less than 4%).

The stock test article suspension will be prepared by suspending the appropriate quantity of test article in the vehicle using a mortar and pestle. Stock and dosing suspensions will be stored at 0 - 4°C. Dosing suspensions will not be analyzed as this is a preliminary dose range-finding test and not a GLP compliant study."

9. Page 5 Section 8.7.4

Change the first food consumption day from 6/7 to 7/8.

Reason: To allow for the gradual feeding regimen as described in section 7.12 to be completed.

10. Page 5 Section 8.7.5

Add "(50 mg/kg)" after "sodium pentobarbital".

Reason: Clarification of the dose of pentobarbital used for euthanasia.

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PROTOCOL AMENDMENT

Study No.: 137

Title: Dose Range-Finding Developmental Toxicity Study of WR242511 in Rabbits

11. Page 6 Section 8.7.7

Add the following sentence: "If any implantation site is detected, the ovaries will be examined as in 8.7.6."

Reason: If pregnancy evidence is confirmed, ovarian changes should be examined.

Approvals:

STUDY DIRECTOR: _____ 12/10/93
Barry S. Levine, D.Sc. D.A.B.T. Date

SPONSOR APPROVAL: _____ 12/13/93.
George J. Schieferstein, Ph.D. Date
Contracting Officer's
Representative (COR)

PROTOCOL AMENDMENT

DRAFT

Study No.: 137

Title: Dose Range-Finding Developmental Toxicity Study of WR242511 in Rabbits

12. Page 1

Add to the title the phrase (Segment II) to read "Dose Range-Finding Developmental Toxicity (Segment II) Study of WR242511 in Rabbits

Reason: More precision in reflecting the nature of the study as discussed with the Sponsor.

13. Page 1 Section 4.0

Add study dates as follows:

| | |
|---|---|
| 4.1 Proposed Initiation of In-Life Phase: | 7/02/94 |
| 4.2 Proposed Completion of In-Life Phase: | 7/26/94 |
| 4.3 Proposed Study Completion Date (Draft Final Report): | 9/26/94 |

Reason: Study dates have been finalized.

14. Page 3 Section 7.6 and Page 4 Section 7.11

Replace Hazleton Research Products, Inc. by HRP, Inc.

Reason: To reflect the correct name.

15. Page 3 Section 7.8

Replace the first three sentences by the following:

"Each animal will be given a facility-unique number (ear-tag) by the Supplier, and a study-unique number (ear-tag) upon arrival at UIC. This latter number will also appear on a cage card visible on the front of each cage."

Reason: Clarification of procedures.

16. Page 4 Section 8.1

A. Add the following dose levels: 0, 0.5, 1, 2.5, 6 and 14 mg base/kg/day.

B. Change the first sentence to indicate the doses will be selected on the basis of a "preliminary range-finding test (Section 8.6a).

Reason: (A) Dose levels have been selected and (B) to clarify a change in procedure.

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Study No.: 137

Title: Dose Range-Finding Developmental Toxicity Study of WR242511 in Rabbits

17. Page 5 Section 8.6

Add the following section:

8.6a Preliminary Range-Finding Test: Two nonpregnant animals/dose (3 dose levels) will be dosed with the test article for up to 13 days. The doses will be selected based on the dose-range finding study in rats (UIC/TRL Study No. 143). Doses may be adjusted during the treatment period to demonstrate toxicity. Clinical signs will be recorded daily. Body weight and food consumption will be collected at pretest and approximately on days 0, 4, 7, 10, and 13.

Reason: To aid in selection of dose levels.

18. Page 5 Section 8.7.3

Replace Day 30 with Day 29.

Reason: Clarification of procedures. Day 30 could result in a few litters being born prior to C-section.

19. Page 6 Section 8.7.5

Replace Day 30 with Day 29.

Reason: Clarification of procedures. Day 30 could result in a few litters being born prior to C-section.

20. Page 7 Section 8.8.10

Add the following section after the first after the first paragraph.

The mean numbers of resorptions, nonviable fetuses, viable fetuses, corpora lutea (C.L.), implantations, preimplantation loss* and postimplantation deaths** will be compared using the Kruskal-Wallis test. If a significant effect is seen ($p \leq 0.05$), the Mann-Whitney U test will be used for pairwise comparisons to the control group.

*Preimplantation loss = # C.L. - # implantations

**Postimplantation death = # implantations - # live fetuses

Reason: Clarification of statistical analyses procedures.

Approvals:

STUDY DIRECTOR: Barry S. Levine, D.Sc. D.A.B.T. 7/1/94 Date

SPONSOR APPROVAL: George J. Schieferstein, Ph.D. Contracting Officer's Representative (COR) 7/19/94. Date

# APPENDIX 5

Study Deviations

DRAFT

Contract No.: DAMD17-92-C-2001
Task Order No.: UIC-7M
Study No.: 137

# DOSE RANGE-FINDING DEVELOPMENTAL TOXICITY (SEGMENT II) STUDY OF WR242511 IN RABBITS

## Study Deviations*

| Deviation Type | Specific Deviation | Effect on Study |
|---|---|---|
| Protocol | Temperature was out of range on several occasions during the preliminary study in non-pregnant animals. | None, the changes were minimal. |

* The detailed "Deviation Reports" are contained in the raw data which are archived at the University of Illinois at Chicago, Department of Pharmacology, Chicago, Illinois.

The above deviations did not affect the integrity of the study.

_____
Barry S. Levine, D.Sc., D.A.B.T.

_____
Date